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Electrophysiological Studies of Nerve and Reflex Activity in Normal Man.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

IV. The Two-Neurone Reflex and Identification of Certain Action Potentials from Spinal Roots and Cord[1, 2]

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Although, as Renshaw (1940) pointed out, monosynaptic arcs of two neurones have been embodied in earlier suggested patterns of mammalian spinal reflex activity (Cajal, 1909; Creed et al., 1932), it is only in the last ten years that their presence has been clearly demonstrated. Renshaw (1940) recorded in cats central delays in some instances as short as 0.5 millisecond—values compatible only with the interposition of a single synapse (Lorente de Nó, 1938). He was quick to grasp the significance of the observation and indicated the possibility of assessing motoneurone excitability under various conditions by testing it through this direct channel. In a series of investigations over the subsequent years Lloyd (1943a, 1946) has firmly established in cats the importance of the two-neurone arc in the reflex response to brief stretch. He demonstrated its afferent limb from muscle in those fibres of lowest threshold and highest conduction velocity which he designated Group I (Lloyd, 1943a). Furthermore, his analysis of factors conditioning motoneurone discharge when tested by these highly-organized two-neurone reflexes has provided a sound basis for a wide variety of mammalian reflex studies (Lloyd, 1946).

Comparable investigations have not been carried out in intact man. For apparent reasons it is not possible to stimulate or record directly from sharply localized regions of peripheral pathways or spinal cord. Nevertheless, in order to interpret factors in human function on the basis of more exact, and by their very nature more artificial, animal studies, it is necessary to establish that comparable patterns exist in both. Hoffmann (1918) made strides in that direction by demonstrating that human ankle and knee "jerks" were accompanied by sharp spike action potentials in the appropriate muscles, whose form and approximate latency (after allowing for nerve conduction time) were comparable to those evoked by submaximal electric shocks to the skin overlying posterior tibial and femoral nerves respectively. His deduction that

[1] Supported by grants from the Lewis J. and Harriet S. Lederer Fund of The Johns Hopkins Hospital and from the National Institutes of Health, U. S. Public Health Service.

[2] Part of this material was presented to the Association for Research in Nervous and Mental Disease on 15 December 1950.

the afferent impulses of these reflexes were of low threshold and high velocity was recently confirmed when it was shown that their conduction rates were greater than those in the corresponding motor axones (Magladery and McDougal, 1950). In both series of studies, however, details of central delay were lacking by virtue of the purely peripheral recording used. Pool's (1946) demonstration that insulated recording electrodes could be placed within the spinal theca of paraplegic patients indicated, however, the possibility that

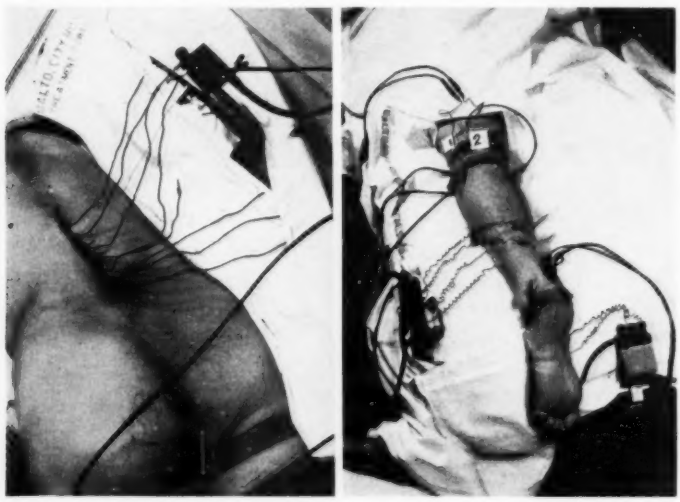

FIGURE 1

Photographs of experimental arrangement. On the right, small placards have been placed over stimulating electrodes: 1, 3—paired needles inserted in or near peroneal and plantar nerves respectively; 2—monopolar surface stimulation over posterior tibial nerve.

In right hand picture, paired surface recording electrodes can be seen in place over anterolateral, calf, and small foot muscles. In the picture on the left, insulated needles for spinal root and cord recording have been inserted into thecal sac.

information about central events in man could be obtained by this means. In the present paper activity recorded from such intrathecal electrodes has been correlated with that obtained from skeletal muscle following excitation of mixed nerve trunks of low threshold.

PROCEDURE

The subjects were normal young adults and volunteers from older age groups showing no evidence of neurological disease affecting spinal cord or limbs under investigation. The arrangement for electrical stimulation of mixed peripheral nerve trunks through skin with monopolar cathodal shocks of low intensity has been described previously (Magladery and McDougal, 1950). Whenever higher stimulus intensity was needed, and therefore the likeli-

hood of pain or spread to nearby nerve trunks greater, shocks were delivered through paired needle electrodes inserted in or near the nerve trunk. Muscle tension and afferent discharge was varied in certain instances by passive manipulation of the limb or by mechanical tapping of skin overlying tendon or muscle belly.

Muscle action potentials were led to amplifiers and cathode ray oscilloscope through paired electrodes fixed to the skin overlying muscles (Fig. 1). Since Hodes, Larrabee and German

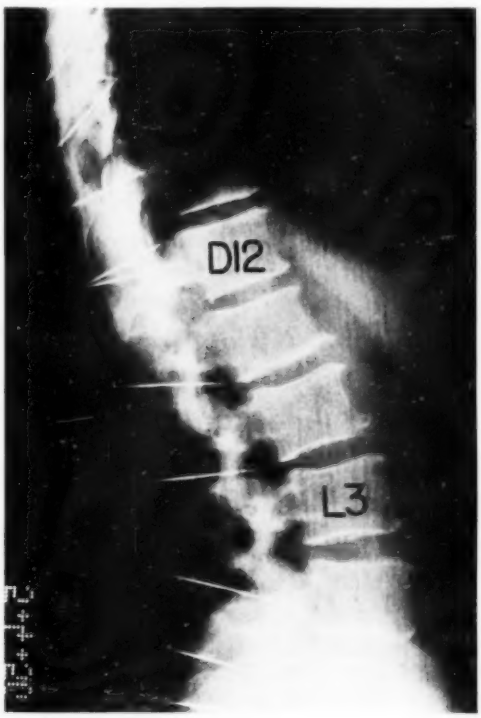

FIGURE 2

Lateral roentgenogram of spine taken at conclusion of an experiment. Tips of active insulated needle electrodes in thecal space at various spinal levels.

(1948) have pointed out that action potentials of nearby muscles, though of reduced amplitude, are also detected by such electrodes, comparison was always made with deflections recorded through similar electrodes placed on adjacent and opposite surfaces of the limb.

Action potentials from spinal roots and cord were similarly recorded at much higher amplification through bared tips of long insulated steel needles placed within the spinal theca through various interspaces below the 9th dorsal (D 9) vertebral level (Fig. 1). Of a series of needles inserted in this fashion, some invariably recorded no activity following peripheral nerve stimulation. One of these was used each time as a relatively indifferent electrode. The situation of the critical electrodes was known fairly accurately by clinical

experience but was checked by roentgenograms (Fig. 2) at the end of each experiment. By this means it was possible to know at what level the electrode was lying in the volume conductor, but little further accuracy in localization was possible. It could not, for instance, be determined whether a specific needle tip lay anterior or posterior to any particular set of spinal roots in the lumbar region. Cautious placement, however, made it almost certain that the more cranially-situated electrodes lay dorsal to the spinal cord. At the completion of the experiment, the distance from the point where each critical electrode pierced the skin was measured to a fixed bony point in the mid-line. By comparison with the roentgenograms, and then subtraction, distances between electrode tips were calculated. In these investigations, administration of sodium phenobarbital achieved a degree of drowsiness in which random voluntary muscle action potentials from the back did not interfere too greatly. This degree of sedation had no detectable effect on any of the peripheral manifestations of reflex activity.

Ischemia, when employed, was produced by a sphygmomanometer cuff placed around the thigh. This was inflated to, and maintained at, a pressure of 200 mm. Hg for the necessary period of time.

RESULTS AND INTERPRETATIONS

A. Peripheral manifestations

The potential changes described by Hoffmann (1918) have been obtained from calf, hamstring, and quadriceps muscles following tendon tap or submaximal stimulation of the mixed nerve supplying the muscle. They were not evoked in these muscles when other nerves of the region were stimulated, and have never been encountered in anterolateral muscles nor in small muscles of the foot following shocks to peroneal or plantar nerves. The potentials have been designated for descriptive purposes as those of *H reflexes* (Magladery and McDougal, 1950). In view of the relative ease with which it has been obtained following stimulation of the posterior tibial nerve in popliteal fossa, the H reflex to calf muscles has been more extensively studied than that to the other leg muscles. Action potential size varied slightly in certain experiments. In others it was remarkably constant. This variability in the lowest-threshold myotatic reflex has also been encountered in animals by Lloyd (1943c), Granit (1950), and others.

Figure 3 illustrates typical action potentials of the H reflex in calf muscles comparable to those described in the first paper of this series. Intensity of nerve stimulation was progressively increased throughout the sequence of records. It is apparent that 32 milliseconds after liminal stimulation (records 1 and 2) a single deflection was recorded—that of the H reflex. With slightly stronger shocks the H deflection increased in amplitude and an additional action potential, labelled M, appeared some 19 milliseconds earlier. This new activity in muscle was evoked by impulses in some efferent motor axones which, with the stronger stimuli, were activated in addition to an increased number of afferent fibres. The H potentials reached maximal size with only moderate stimulation intensity. With yet stronger shocks, as shown by suc-

ceeding records of the figure, the motor deflection increased to a maximal value (record 7) whereas the reflex response dwindled, then vanished.

This relationship of H amplitude to stimulus intensity was a constant feature of this experimental arrangement. As already pointed out by Hoffmann (1918), reduction in size of reflex response with increasing stimulus strength likely indicates a blocking effect in axones or somata by antidromic impulses in motoneurones. This explanation, on which deductions of high afferent

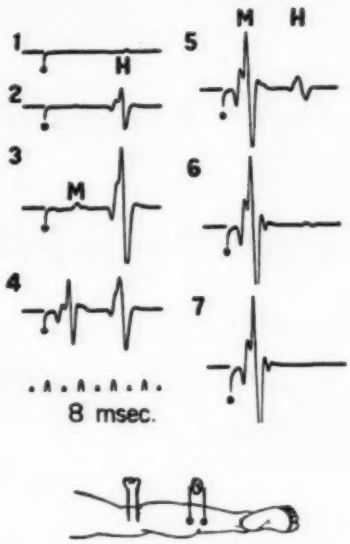

FIGURE 3

Action potentials from calf muscles. Surface electrodes. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Stimulus artefact in this and subsequent figures indicated by small dot. Largest M deflection about 6 mV. See text.

velocity and short central delay are based, has been subjected to actual test by investigation of more central electrical patterns evoked by similar peripheral nerve stimulation.

B. Intrathecal Manifestations in Lumbar Region

In Figure 4 are illustrated action potentials recorded from a needle electrode placed at L 5 vertebral level within lower lumbar theca. The posterior tibial nerve was stimulated by successively stronger shocks comparable in intensity to those producing the tracings of Figure 3. Amplification, however, was about 500 times that used in the muscle records, and size of the action potentials did not greatly exceed that of random deflections. For additional clarity,

therefore, multiple sweeps of the cathode ray beam were also photographed on a single frame (Dawson, 1947). Tracings of single and multiple sweeps are shown respectively in the left and right hand columns of the figure.

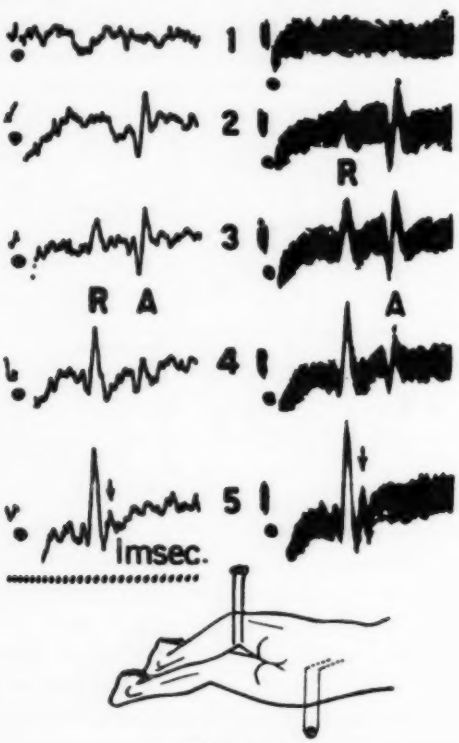

FIGURE 4

Spinal root action potentials. Needle electrodes at L 5 level. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Records in right hand column have 25 sweeps of cathode ray beam superimposed. Those on left are single tracings of the same events. "A" indicates anterior root discharge. "R" is dorsal root deflection due to synchronous Group I afferent volleys. Arrow signifies spike potential produced by antidromic impulses in motor fibres. Amplitude of largest R deflection about 40 microvolts.

With subthreshold stimulation, activity was random (record 1). With liminal stimuli (record 2) a prominent triphasic action potential appeared about 17 milliseconds after the stimulus artefact. This, labelled A in later records, had an amplitude of about 30 microvolts. With stronger shocks, as seen in succeeding tracings, an additional deflection (marked R) became evident 6 milliseconds before A. A reached its maximal amplitude with only moderate stimulation

intensity (record 3). Slight successive increases in stimulus strength (records 4 and 5) caused it to decrease, then disappear. The earlier R potential, on the contrary, increased progressively in size throughout the course of the same records. It should be noted in record 5, with stimulation strength which just obliterated the A deflection, that the R potential was followed, about 1.5 milliseconds later, by a small sharp spike indicated by an arrow in the figure.

The action potentials of Figure 5 were obtained from the same experiment. They were recorded, however, from a higher (L 3) vertebral level. As noted at the lower site, the A deflection was caused, though with a latency decreased

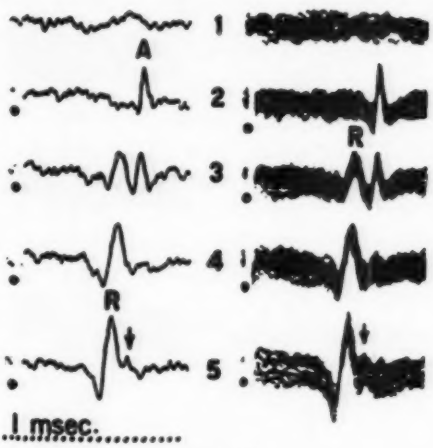

FIGURE 5

Spinal root action potentials. Needle electrodes at L 3 level. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Same amplification as in Figure 4.

to 15.5 milliseconds, by liminal nerve stimuli (record 2). It likewise decreased in amplitude, then disappeared, with successively stronger shocks (succeeding records). With these increasingly stronger nerve volleys, R appeared and increased progressively in size. It preceded A, however, by only about 2.5 milliseconds at this recording site. Once more (as seen in record 5) an even stronger stimulus produced a small spike which followed the R deflection by 1.5 milliseconds.

The records illustrated in Figure 6 were obtained from a yet higher level—L 1. They were similar, in many respects, to those in Figures 4 and 5. The A deflection was the first to appear with minimally effective nerve stimulation, after a latency of only 14.5 milliseconds (record 2). Its amplitude was somewhat greater in record 3, but it decreased successively with the stronger nerve volleys which produced the final two records of the figure. In contrast to the

findings at the lower lumbar sites, however, a deflection with this latency never totally disappeared. Records 3, 4, and 5 depict the concomitant emergence and successively increased size of the R potential. At this level, R was separated from A by only 1.5 milliseconds. This time interval, it will be recalled, was identical with that by which, with stronger nerve volleys, the small unnamed spike followed the R deflections at the lower recording sites.

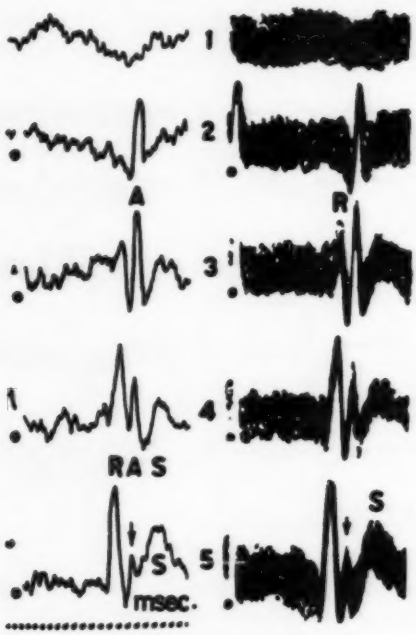

FIGURE 6

Spinal root and cord action potentials. Needle electrodes at L 1 level. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. S deflection is negative internuncial potential from dorsum of cord caused by Group II volleys. Same amplification as in Figure 4.

A later negative deflection of increasing prominence can also be seen in the final three records of Figure 6. It has been labelled S in tracings 4 and 5. It has never been detected in records from lower lumbar levels. It was different in configuration from the earlier potential changes—gradual in onset and considerably longer in duration. Further reference to this S wave will be made later. At this point, however, it should be noted that it appeared (record 3) with the same stimulus intensity as the R potential, and that both deflections increased comparably in size with successively stronger nerve volleys.

The time relationships of the action potential components at the three lumbar levels (Fig. 4, 5, and 6) aid in their identification. It is apparent that the higher the recording site, the shorter was the interval between the R and A deflections—the only action potentials clearly identified at all levels. At L 5, they were separated by 6 milliseconds, whereas at L 1 (termination of spinal cord in man), the interval was merely 1.5 milliseconds. They must therefore have indicated activity moving in opposite directions in fibre pathways streaming down from spinal cord.

Since only the *second (A) deflection* appeared with weak nerve stimuli which produced no detectable direct "motor" effect in muscle (records 1 and 2, Figure 3), it is reasonable to assume that it represented *reflex outflow through anterior roots* in response to an afferent nerve volley. Its decreased latency at successively higher recording sites is in keeping with that interpretation. Failure by our methods to detect dorsal root activity with this low stimulus intensity is readily compatible with Lloyd's (1943a) observation that this low-threshold Group I reflex discharge reaches almost full value with considerably submaximal dorsal root volleys. Decreased amplitude and then final obliteration of the A deflection with successively stronger peripheral nerve volleys must indicate that the reflex discharge was blocked by antidromic impulses in motor axones somewhere proximal to the recording electrodes.

Emergence of the *earlier (R) potential* only with increased intensity of nerve stimulation, and its longer latency when recorded at successively higher sites, might be interpreted in one of two ways. On the one hand, R might indicate centripetal conduction of the antidromic impulses in motor axones to which reference has just been made. Alternatively, the deflection might equally well have been produced by a synchronous volley of *afferent impulses in dorsal roots*. There is considerable evidence to show that the latter is the correct explanation. In this evidence, the tracings of Figure 6 are of considerable importance. The recording site was at L 1 level, approximately at the termination of spinal cord. In record 3, shock intensity was just sufficient to cause the first indication of an R potential and also of a later, more prolonged, S wave. In the subsequent records, with successively stronger nerve volleys, both these deflections increased similarly in size. The S waves will be identified later in this paper with the negative dorsal cord potentials first described in cats by Gasser and Graham (1933) and caused only by afferent volleys. Appearance then, of R deflections with stimulation intensity just adequate to produce S waves suggests that the former also resulted from impulses in afferent nerve fibres.

This suggestion has been strengthened by the use of limb ischemia which blocks conduction in the low-threshold afferent limb of the H reflex at a stage of anoxia when conduction in motor axones is apparently unaltered (Magladery, McDougal and Stoll, 1950). Ischemia of less than 20 minutes obliterated, in all of four experiments, the H waves from calf muscle at the same time that both

the R and S waves disappeared from the intrathecal records. At this stage of ischemia, latency and configuration of motor deflections, and voluntary power, in muscle were unaltered and it is reasonable to assume that antidromic conduction in axones would have been unimpaired. It seems probable therefore that the R deflections, so readily abolished, were not associated with antidromic impulses in motor axones but indicated conduction in dorsal roots of synchronous afferent impulses.

Attention has already been called to the *small spike potential* indicated by an arrow which appeared, but only with the stronger mixed nerve volleys, at the same interval following the R deflection at all three recording sites. Increasing latency of the small spike at successively higher levels, and the constancy of its separation from the R deflection, indicates that it too represented centrip-

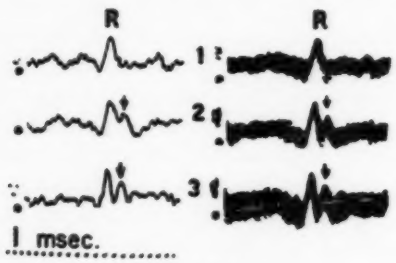

FIGURE 7

Spinal root action potentials. Needle electrodes at L 5 level. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. In record 1, stimulation was already sufficiently strong to produce only small anterior root discharge and dorsal root potential of near-maximal amplitude. Records 2 and 3 show increase in antidromic spike potential with yet stronger volleys.

etal conduction of a volley of impulses. The very fact, however, that conduction time of the higher-threshold volleys was about 10 per cent greater than that of the impulses producing R, implies participation of different fibres. Further distinction between the two components was found when peripheral nerve stimulation was made even stronger (though still not painful to the subject). The tracings of Figure 7, for example, were recorded at L 5 level. In record 1, stimulation was already sufficiently intense that the reflex discharge (A) was almost totally blocked and the dorsal root (R) deflection virtually maximal. Stronger nerve shocks, as illustrated in records 2 and 3, added little to the configuration and size of R. The later small spike, marked by the arrow, however, increased successively in amplitude throughout those records. It has been repeatedly demonstrated in cats by Lloyd (1943b) and others that the group of nerve fibres of lowest threshold and most rapid conduction are afferent, and subserve myotatic reflexes. Impulses in motor axones are initiated only

by stronger stimulation, and they are conducted more slowly. Magladery and McDougal (1950), though in a less exact fashion, made similar observations in man. When the intrathecal records are considered in the light of that information, there can be little doubt but that the small spike potential indicated *antidromic impulses in motor axones*. Failure to detect action potentials of antidromic volleys following less intense stimuli, despite indication of their presence by block of reflex discharge, has not been explained. A similar phenomenon was encountered by Magladery and McDougal (1950) in peripheral nerve trunks from which satisfactory sensory nerve action potentials were recorded, though no signals of antidromic impulses could be detected. Reasons were given in that communication for attributing greater temporal dispersion to antidromic impulses than occurred with afferent volleys.

Identification of the antidromic spike potential casts further light on the records of Figure 6 where recording took place at tip of spinal cord. It has already been noted that, despite increasingly strong nerve stimulation, the deflection labelled A was never abolished. Likewise, in the records of that figure, there was no indication of a separate small spike potential. The explanation of both seeming anomalies appears to be that, at the termination of spinal cord, the reflex discharge (A) and the small spike of the antidromic volley both followed the dorsal root deflection (R) by the same interval—1.5 milliseconds. In fact, what appeared at first glance to be persistence of reflex discharge in the final record of Figure 6, was in reality the development of the antidromic volley.

Of importance is to note that at the termination of spinal cord, the dorsal and anterior root deflections were separated by only 1.5 milliseconds. When allowance is made for conduction in proximal portion of roots and within cord itself, it is apparent that very little time was available for central delay. Whereas the data here presented are inadequate for more detailed analysis, the analogy to the monosynaptic myotatic reflex which Lloyd (1943a) has studied in cats is drawn very close. In his experiments, 0.3 millisecond was attributed to conduction in motor axones proximal to recording electrodes. A comparable value could be assigned to afferent conduction central to that point. It would seem reasonable to assume that in man conduction in central portions of fibres would take at least as long as in cats. By permissible subtraction, therefore, a value of no more, and probably less, than 0.9 millisecond could justifiably be attributed to central delay. This value is in reasonable agreement with that which he, and others, have attributed to transmission across one synapse.

In man, then, successively stronger shocks to posterior tibial nerve in popliteal fossa produced a characteristic pattern of response. With liminal stimulation, a few low-threshold afferent fibres of the highest velocity were activated and caused monosynaptic reflex discharge of motoneurones. This was

detected in muscle as the H response, and from anterior roots as the A deflection. Somewhat stronger nerve stimuli produced a sufficiently synchronous afferent volley to permit ready detection as the R potential from dorsal roots. Those afferent impulses not only effected monosynaptic discharge of segmental motoneurones but also initiated electrical activity in spinal cord itself (S waves) to which reference will be made later. That some antidromic impulses were produced by stimuli of this intensity was indicated by considerable block, proximal to the recording electrodes, of the reflex discharge, and hence decrease in size of the H and A deflections. Dorsal root (R) potentials reached maximal amplitude with only moderate stimulus intensity. Stronger stimulation merely activated more and more motor axones. The motor response (M) in muscle

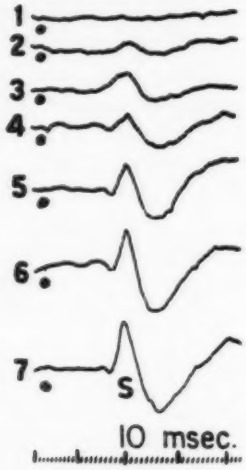

FIGURE 8

Dorsal spinal cord action potentials. Needle electrodes at D 11 level. Single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Amplitude of largest negative S deflection about 80 microvolts. Time intervals, 1 and 10 milliseconds.

grew to its maximal value, and antidromic volleys became sufficiently large and synchronous to block all reflex discharge and to be detected from anterior roots as spike deflections.

C. Intrathecal Manifestations in Lower Dorsal Region

The action potentials of Figure 8 followed single nerve shocks of increasing intensity, and comparable in strength to those which have been used in the previous sections. They were recorded, however, from needle electrodes placed intrathecally at D 11, well above the termination of spinal cord and dorsal to the lower part of the lumbar enlargement. In this region of the back interference from voluntary, or reflexly-induced, action potentials from adjacent muscles was always less than in the lower lumbar region. Use of multiple

sweeps was therefore not usually necessary to aid in detection of intrathecal activity.

With subthreshold stimulation (record 1) no induced action potentials were recorded. With liminal shocks (which, it will be recalled, also evoked the first detectable dorsal root (R) potentials) a small prolonged negative (upward) deflection appeared (record 2). It was followed by a somewhat similar positive (downward) dip below the baseline. With successive increase in stimulus intensity (succeeding records) both waves increased in amplitude but the over-all duration of the combined negative and positive deflections remained much the same—about 17 milliseconds. In the final tracing of Figure 8 the negative potential lasted 6 milliseconds, the positive deflection about 11 milliseconds. These values are fairly representative of the findings in all other experiments. Whereas durations have sometimes been a little greater or less, the positive potential has always lasted about twice as long as the negative deflection. The type of onset of the negative potential has varied too greatly from experiment

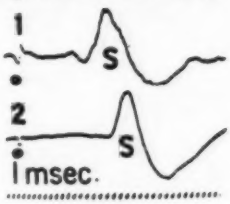

FIGURE 9

Dorsal spinal cord action potentials. Single maximal shocks to same site over posterior tibial nerve in popliteal fossa. In record 1, needle recording electrodes at D 12, in record 2 at D 10, vertebral levels. Interelectrode distance—9 cm.

to experiment to merit much comment. Sometimes, as in Figure 8, there has been an initial positive dip. In other experiments, a small negative spike has appeared in this position. Many times the first change in potential has been that of the upstroke of the negative deflection itself. Likewise, the electrical pattern following the positive potential has been found variable. Sometimes, the return was to an isoelectric state. Usually, however, as illustrated by the records of Figure 8, there has been a prolonged phrase of late negativity, often separated from the termination of the positive potential by a break in continuity.

These negative and positive action potentials were readily detected, following posterior tibial nerve stimulation, over several segments of spinal cord. With electrodes at L 1 vertebral level (Fig. 6), they were usually found—occasionally they appeared at D 9. They were most prominent, however, over the intervening region of cord. There was no consistent alteration in size of the deflections at the increasingly higher levels. There was, however, a successive increase in latency. This is illustrated in Figure 9. The records were

evoked by nerve shocks to the same site in popliteal fossa. In record 1, the deflections were recorded from D 12 level after a latency of 13 milliseconds. In record 2, with electrodes placed at D 10, the latency was 16 milliseconds. The interelectrode distance was approximately 9 centimetres. In this experiment, therefore, the potentials moved upwards at about 30 metres per second before disappearing. This rate of movement is fairly representative of all such experiments in which the extremes were found to be 15 and 40 metres per second.

When a stimulus to posterior tibial nerve was of sufficient intensity to evoke maximal dorsal root (R) and spinal (S) deflections, a refractory period was

FIGURE 10

Dorsal spinal cord action potentials recorded at D 11 level. Maximal shocks to posterior tibial nerve in popliteal fossa at intervals shown by dots of stimulus artefacts. In record 4, arrow indicates discontinuity in downstroke, mentioned in text, of first negative potential. Time intervals, 1 and 10 milliseconds.

evident following both potentials. For technical reasons, the characteristics of this have not yet been completely clarified. The pattern, however, is indicated in Figure 10. In the experiment illustrated, a second maximal nerve shock was delivered at different intervals after the initial maximal stimulus. When stimulus separation was 25 milliseconds (record 1) or more, the configuration of the second spinal potentials was normal. At an interval of 17 milliseconds (record 2) the negative deflection of the second response was still unchanged although the positive component was slightly diminished. In record 3, the separation was 9 milliseconds—both the negative and positive potentials evoked by the second stimulus were greatly reduced in amplitude. At shorter intervals, they

decreased further in size and when the second shock followed the first by 2 milliseconds (record 4), they were only detectable as a break marked by an arrow in the downstroke of the first S wave. When the stimuli were even closer together, the deflections were merely those produced by the first shock. The presence of the deep positive potential produced by the first nerve volley introduces difficulties in interpreting the decrease in the second potentials, and makes accurate assessment of time course impossible. It has seemed best therefore at this point simply to indicate the existence of the phenomenon.

It has already been shown that submaximal stimuli to the posterior tibial nerve which were followed by R deflections and caused strong monosynaptic responses, also produced S potentials (record 3 of Figure 6). That is not in

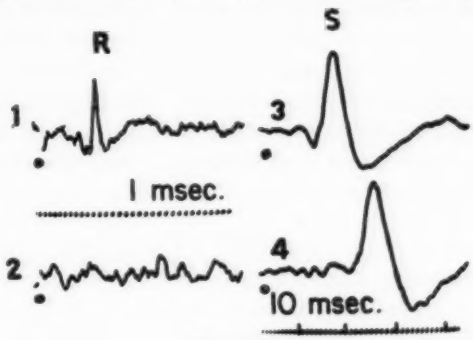

FIGURE 11

Action potentials from spinal roots and dorsum of cord. In records 1 and 2, recording electrodes (root) at L 4 level. In records 3 and 4, recording electrodes (cord) at D 11 level. Single submaximal shocks to posterior tibial nerve in posterior fossa in records 1 and 3. Single maximal shocks to plantar nerve at ankle in records 2 and 4. See text. Time intervals, 1 and 10 milliseconds.

any way to imply that the R deflections and monosynaptic reflexes on the one hand, and the S potentials on the other, were causally related. Indeed the contrary may be suggested by Figure 11. In the experiment which it illustrates, records 1 and 2 were obtained from electrodes placed at L 4; records 3 and 4 from similar needles at D 11. For the upper two tracings, the posterior tibial nerve was stimulated in the popliteal fossa. This produced a prominent dorsal root deflection (record 1) and the usual spinal negative and positive potentials (record 3). Muscle action potentials of the monosynaptic reflex (not shown) were present peripherally. When, however, the plantar nerve was stimulated at the ankle, evidence of this low-threshold reflex has never been detected in the appropriate small foot muscles. Electrodes in the lumbar region (record 2) showed, as in all similar experiments, only random activity. If therefore low-threshold, high-velocity, Group I fibres were excited in the plantar nerve, the

impulses were not sufficiently numerous or synchronous to cause detectable dorsal root (R) potentials or to discharge a monosynaptic reflex. Yet record 4 shows that spinal cord potentials, of increased latency but otherwise similar in every way to those already described, were produced. Apparently then, comparable S potentials were produced by afferent volleys in nerves which differed only in that one of them contained detectable low-threshold impulses of two-neurone arcs. It would seem likely, therefore, that these Group I impulses did not in either case cause the S potentials.

In brief then, afferent nerve volleys, just sufficiently strong and synchronous to produce detectable dorsal root (R) deflections, also caused distinctive slow action potentials in the dorsum of spinal cord. Similar slow action potentials, however, resulted from afferent volleys in nerves wherein no evidence of Group I activity could be detected. The potentials consisted of negative and positive components which were propagated cranially for several spinal segments at a velocity of about 30 metres per second. They were followed by short absolute, and prolonged relative, refractory periods. The prominent components were sometimes preceded by small sharp deflections, and usually followed by prolonged periods of late negativity.

DISCUSSION

The purpose of the present communication has been to delineate more sharply the reflex responses in man which Hoffmann (1918) first produced electrically and compared with those evoked by mechanical tap on certain tendons. These responses have been detected in the leg only from quadriceps, hamstring, and calf muscles. They are represented therefore in both extensor and flexor groups. The muscle action potentials of the reflex reached maximal size with only weak nerve shocks. Figure 3 shows that they could be produced with no detectable excitation of motor axones. The reflex must therefore have resulted from impulses in afferent fibres of low threshold, and hence high velocity (Erlanger and Gasser, 1937). This feature is shared in common with the response to a light tendon tap and serves to identify the reflex with a two-neurone myotatic arc (Lloyd, 1943a). With increasing strength of stimulation, however, motor axones were also excited and, when sufficient antidromic impulses passed centrally in these fibres, the reflex discharge to muscle was blocked (Figure 3).

Certain of these features which were detected or assumed from peripheral studies, have been clarified by more central recording from spinal roots and dorsum of cord. That activation of only a portion of the low-threshold afferent fibres was sufficient to produce a synchronous discharge from anterior spinal roots, has been demonstrated by recording action potentials of the latter (A deflections) when dorsal root activity was insufficient or too dispersed for detection. This massive synchronous reflex discharge by submaximal dorsal

root volleys (Lloyd, 1943b) emphasizes another feature shared by both H reflexes of man and two-neurone arcs in cats. Complete identification, however, has resulted from demonstration that the interval between dorsal and anterior root deflections of the reflex at the tip of spinal cord was of the order of 1.5 milliseconds. Reasonable deduction for intraspinal conduction leaves only 0.9 millisecond (and probably less) for central delay; a value compatible only with passage across a single synapse (Lorente de Nó, 1938).

Recognition of the spike potentials produced in anterior roots by antidromic volleys in motor axones has enabled direct comparison of the relative velocities, in man, of impulses in the afferent and efferent limbs of the monosynaptic arc. Previous comparisons have, of necessity, been based on latency differences in muscle action potentials when the nerve trunk was stimulated at two separate points. Errors in determination of exact sites of stimulation were, therefore, doubly reflected in the calculated velocities. Using this indirect method, for example, Magladery and McDougal (1950) found that the low-threshold afferent fibres conducted impulses about half again as rapidly as the motor fibres. In reality, as shown by the present more direct measurements, the difference in velocity is one of only ten per cent. In view of the discrepancy in this instance, it is quite likely that other comparative values determined by means of the indirect method may also be less accurate than was thought at the time. It seems advisable, for the present, to consider them as only approximate until substantiated by more accurate means.

The dorsal spinal cord action potentials were clearly similar to those first described in cats by Gasser and Graham (1933) and designated by them as "intermediary potentials." The present deflections have been recorded only from electrodes placed dorsal to spinal cord—never has there been sufficient spread for detection from roots. The rising phase of the negative deflection was always relatively gradual—the usual time from onset to crest was about 2 milliseconds. Its duration was generally about 8 milliseconds although, in different subjects, this varied from 6 to 12 milliseconds. With increasing stimulus intensities, the succeeding positive potential became more and more prominent and indeed appeared to sharpen the decline of the negative deflection. The potentials were detectable only over a few segments of the spinal cord and, in that region, were propagated cranially at approximately 30 metres per second. All these features are comparable to those described by Gasser and Graham (1933) and support the presumptive identification.

In the presence of the large negative and positive intermediary potentials, deductions concerning subsequent refractory periods must be only tentative. Reduction in size of the deflections evoked by a second maximal nerve volley may well have been governed by other factors than refractoriness. Nevertheless, at a stimulus interval of 2 milliseconds (record 4 of Fig. 10), a separation at which Gasser and Graham (1933) showed considerable recovery of excitability

of primary afferent intraspinal neurones, a potential added by the second volley first appeared. The absolute refractory period of the neural components producing the intermediary potentials must, then, have been short. Time of the subsequent recovery to normal excitability was, however, quite long. In these experiments, size and configuration of potentials evoked 25 or more milliseconds after those due to a first nerve volley appeared normal. This period of subnormality still was considerably less than that described in cats by Gasser and Graham (1933).

There has been no consistent indication, within spinal cord, of sharp potentials which could be attributed to synchronous impulses in primary afferent pathways. It is true that in some experiments a small negative or positive deflection was discernible at the beginning, or on the ascending limb, of the prominent S waves. Its latency was only little greater than that of the dorsal root (R) action potential which was detectable only as high as L 1. It likely therefore, indicated higher, intraspinal, activity in the same neurones. Its variability, however, from experiment to experiment, and its inconstancy at different levels over dorsum of spinal cord, prevented a close analysis of its conduction rate or extent of spread. Gasser and Graham (1933), on the other hand, clearly identified the primary afferent contribution to the intermediary potentials in a consistent sharp preceding spike, and demonstrated that conduction and excitability changes in that afferent pathway were compatible with those of a primary neurone. They also showed that the intermediary potentials were unrelated to motoneurone activity. Antidromic volleys in motor axones neither produced demonstrable deflections nor influenced the orthodromically-induced cord potentials. By exclusion, therefore, Gasser and Graham (1933) suggested that the intermediary potentials which they described indicated interneurone activity. This interpretation has been generally accepted (Hughes, McCouch and Stewart, 1937; Eccles, 1939; Bremer, 1947; Brooks, Downman and Eccles, 1950) and almost certainly applies to the S potentials described in this communication. Subsequent animal experiments have shown that these internuncial, and other slow spinal potentials are related to synaptic activity. Their negative and positive components correspond, respectively, to increased and decreased excitability of spinal neurones (Gasser and Graham, 1933; Hughes and Gasser, 1934; Bremer, Bonnet and Moldaver, 1942; Eccles, 1946; Bernhard, 1947).

The type of afferent discharge causing these intermediary, or internuncial, potentials in man has been of particular interest. It was clearly shown that they followed afferent volleys in nerve trunks which were considerably different in their reflex potentialities. Since the potentials occurred after stimuli to the plantar nerve which produced no detectable monosynaptic reflex, they presumably were not due in that instance, to impulses in low-threshold Group I afferent fibres. It seems reasonable to infer, therefore, that the internuncial

potentials which followed submaximal shocks to the posterior tibial nerve were likewise not due to impulses in Group I fibres, although the latter were demonstrably activated at the same time. Lloyd (1943c) has already shown in cats that it is difficult, even with stimulation of afferent nerves from muscle, to obtain a pure Group I afferent volley. With all but the weakest of shocks, Group II fibres are also activated and cause internuncial potentials. A similar situation probably exists in man. With the weakest stimuli only Group I discharge occurred. With stronger shocks, other fibres were also excited, and impulses in those fibres caused the internuncial activity. Since, therefore, total volleys in these physiologically different fibres cannot be differentiated on a basis of threshold to this form of stimulation, it has seemed best, hereafter, to adopt arbitrarily the nomenclature of Lloyd (1943b) in describing them. Group I volleys are those producing two-neurone reflexes. Impulses in Group II fibres cause detectable internuncial activity.

The degree to which fibre thresholds in the two groups overlapped has, however, been found greater than would have been expected from the animal experiments. Certainly only very submaximal monosynaptic reflex discharges occurred before Group II impulses became apparent. Internuncial potentials, for instance, were quite discernible in Figure 6 before anterior root deflections reached their greatest size. This only indicates, however, the upper range of the overlap, as antidromic block limited the completeness with which we were able to record the anterior root discharge. A better indication was obtained by noting the progressive increase in size of the dorsal root (R) deflection in Figures 4, 5, 6 and 7. Since this deflection was not detected when Group II impulses were discharged from the plantar nerve, it may be assumed that, when it occurred, it was mainly due to synchronous Group I volleys. It will be readily noted that when stimulus intensity had become sufficient to produce the maximal dorsal-root (R) deflection, the internuncial slow potentials were already virtually at their greatest size. In man then, with the present methods, it has been found impossible to stimulate all Group I afferent fibres from muscle without at the same time producing a large Group II volley and, by inference (Lloyd, 1943c), one from muscle itself.

It is of considerable interest that such large Group II afferent volleys did not produce detectable dorsal root (R) potentials. That they were not obscured by the action potentials produced by Group I volleys seems probable for two reasons. In the first place, the R deflections reached their maximal amplitude with stimulus intensities well below those producing the greatest antidromic discharge in motor axones, and did not continue, with stronger shocks, to increase in size. Secondly, and perhaps more conclusively, strong Group II volleys from plantar nerve caused no discernible dorsal root deflections. Apparently, then, their absence indicates considerable temporal dispersion, in sharp contrast to the marked synchronism of Group I volleys.

SUMMARY

Certain features of two-neurone reflexes in man have been described. These have been established by correlating action potentials produced in muscle, spinal roots, and spinal cord following stimulation of afferent fibres in the posterior tibial nerve.

The reflexly-induced deflections in muscle (H waves) were evoked by activation of lowest-threshold Group I afferent fibres. They were blocked, close to (or within) spinal cord, when antidromic impulses were discharged in motor axones by stronger peripheral nerve shocks.

Liminal nerve stimulation, which just evoked the H response, produced a detectable anterior root (A) action potential. It increased in amplitude and then declined, in keeping with the reflex muscle potentials. Nerve stimulation of somewhat greater intensity than that evoking the first electrical indication of reflex discharge, produced prominent dorsal root (R) action potentials. These were separated, at the tip of cord, from the anterior root deflections by only 1.5 milliseconds. Reasonable deductions for more central fibre conduction time allow inference that the reflex arc was monosynaptic.

Identification, from spinal roots, of antidromic volleys in motor axones, with latencies greater than those of dorsal root potentials, showed that conduction in motor fibres was ten per cent slower than in lowest-threshold Group I afferent fibres.

Activation of enough Group I fibres to cause detectable dorsal root potentials was always accompanied by considerable discharge of afferent impulses in Group II fibres. These Group II volleys, though sufficiently dispersed that they produced no discernible dorsal root deflections, were followed by slow internuncial potentials recorded from the dorsum of the spinal cord.

These investigations would not have been possible without the experience and help of Dr. S. A. Talbot. Most of the apparatus was designed, constructed, and maintained by him and members of his staff—Mr. T. Arnold and Mr. E. Ramey. The authors thank them warmly.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

V. Excitation and Inhibition of Two-Neurone Reflexes by Afferent Impulses in the Same Nerve Trunk[1, 2]

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Excitability of spinal motoneurones in animals has been investigated in a variety of ways during the last sixty years. In most instances it has been tested by observing, under various experimental conditions, motor responses reflexly produced by some form of afferent stimulation. Responses to muscle stretch or tendon tap, for example, were found to be influenced by tension in other muscles (Sherrington, 1893). Later these methods of conditioning were often replaced by measurable more direct stimulation of various afferent pathways. Observation of the tendon jerk as a test procedure increasingly gave way to more precise recording of electrically-induced reflex responses in muscle. By such means, the Oxford school (1932) elucidated the principles of reciprocal innervation, and brought together integrative patterns whereby reflex discharge in the final common path is modified at a spinal level by facilitation and inhibition.

These methods of assessment, however, lacked exact information on the characteristics of the reflex arc used in testing. Renshaw (1940) first obtained sufficient indication of the monosynaptic nature of low-threshold myotatic reflexes to suggest their use as means of determining directly motoneurone excitability stripped of the variance introduced by lability of internuncial systems. In more recent years Lloyd (1943a, b, c; 1946) has further defined the features of this highly organized two-neurone reflex and clearly demonstrated its dependence on afferent impulses from muscle in Group I fibres of the lowest threshold. This method of determining excitability of motoneurones, when conditioned in differing ways, has since been widely used to advantage in experimental animals by Lloyd himself (1946), Eccles (1946), Bernhard (1947), Brooks and Eccles (1947); Brooks, Downman and Eccles (1950), Granit (1950), and others. Further impetus to the investigation of factors governing facilitation and inhibition of motoneurone discharge was given by

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the demonstration in cats of slow dorsal spinal cord potentials produced by afferent nerve volleys (Gasser and Graham, 1933). These negative and positive deflections (intermediary potentials) were attributed to interneurone activity, and the authors correlated the signs of the potentials with changes in reflex excitability of the cord—negative with increased, positive with decreased, excitability. The broad features of this interpretation and correlation have been generally accepted, though most subsequent studies have been directed towards synaptic changes at motoneurones themselves by analysis of dorsal and ventral root potentials (Barron and Matthews, 1938; Bremer, Bonnet and Moldaver, 1942; Bremer and Bonnet, 1942; Eccles, 1946; Eccles and Malcolm, 1946; Bernhard, 1947).

In man, despite early recognition of the "silent period" (Hoffmann, 1918; Denny-Brown, 1928), little study has been made of facilitation and suppression of motoneurone discharge. Demonstration of a readily-produced two-neurone myotatic (H) reflex, and identification of intermediary potentials from intact human spinal cords (Magladery, Porter, Park and Teasdall, 1951), opened the possibility of making such investigations. It is the purpose of this communication to present observations on the conditioning of motoneurone excitability by afferent volleys in which some impulses produced the two-neurone reflex.

Difficulties and pitfalls associated with a study in experimental animals of conditioning effects of prior afferent nerve volleys on a simple monosynaptic reflex have been stressed by Renshaw (1940), Lloyd (1946), Bernhard (1947), Granit (1950), Brooks, Downman and Eccles (1950), and others. They are related to electrode position, viability of preparations, type and intensity of stimulation, anaesthesia, and so on. Variability in certain of these factors is even greater when the normal human is used. On the other hand, there are advantages in the use of intact, unanaesthetized, preparations when studying processes which may contribute to the total motor response of that individual, provided constant recognition is made of possible sources of error and limitations of accuracy.

PROCEDURE

The experimental procedures, and methods of stimulation and recording, have been described previously (Magladery, Porter, Park and Teasdall, 1951). The monosynaptic (H) reflex to calf muscles resulting from a single submaximal shock to posterior tibial nerve in popliteal fossa has been used to test excitability of its motoneurones following prior stimulation of afferent fibres from those muscles. In these, and subsequent, studies of interaction a rigid requirement has been set up for the test reflex, namely that it must be possible to evoke the H potential in muscle at weak stimulus strength with little or no evidence of an initial "motor" deflection.

RESULTS AND INTERPRETATIONS

It has long been recognized clinically that some degree of muscle relaxation, and an intermediate position of the limb, are usual requisites for detection of

"tendon jerks" in normal persons. In extreme positions, perhaps for different reasons, the responses become unobtainable. Likewise, it is often found that increased voluntary muscle tension makes them more difficult to obtain. At times, however, under just these conditions, they are readily detected. It seems unlikely that any one factor can account for these differences, but afferent discharge from muscle is clearly of importance.

Although investigated by many previously, Granit (1950) has been the latest to study the effect of initial muscle tension on facilitation and inhibition of the monosynaptic reflex of cats. This, it will be recalled, has been identified by Lloyd (1943c) as the most important, at any rate, of the reflex arcs responding to brief stretch. Granit (1950) stressed the predominant effect of stretch in augmenting central inhibition of motoneurone excitability. In man, similar suppression of a monosynaptic reflex to calf muscles has been found by passive flexion or extension of the foot. This is illustrated in Figure 1 where the H

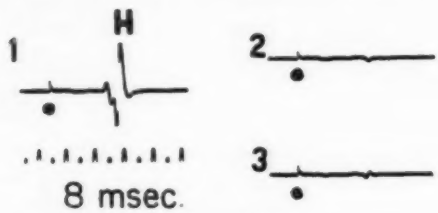

FIGURE 1

Action potentials from calf muscles. Surface electrodes. Single submaximal shocks to posterior tibial nerve in popliteal fossa. Record 1—foot in "neutral" position. Records 2 and 3—foot held firmly by observer in flexion and extension, respectively, at ankle.

reflex of record 1 was virtually abolished, in records 2 and 3, by those maneuvers. Since there is no reason to believe that the electrical depression could be attributed to a purely peripheral condition of muscle fibres, it was probably due to central inhibition resulting from stimulation by stretch of muscle receptor endings (Matthews, 1933; Barron and Matthews, 1938).

A little more refinement was introduced by conditioning the monosynaptic reflex with a "tendon jerk." This was the method which Ballif, Fulton and Liddell (1925) used in early studies of inhibition before the identity of their test reflex as monosynaptic had been established. Figure 2 illustrates this interaction in man. In record 1, the usual deflection of the H reflex is shown. In succeeding records it was tested at different intervals after a light tap on Achilles' tendon. Displacement of the baseline accompanying each blow is indicated by an arrow. Dots designate artefacts of the electrical stimuli to the posterior tibial nerve. It is apparent that a prolonged period of depression succeeded the tendon jerk; no evidence of facilitation was ever obtained. Complete suppression of the test response occurred in record 2 when stimulus sepa-

ration was some 50 milliseconds. At the longer intervals, the reduction was incomplete but, as seen in record 4, a monosynaptic reflex tested 200 milliseconds after the ankle jerk was still far below its control size. No attention may, however, be paid to the time course of these records. It soon became evident that duration of succeeding suppression was dependent on strength of conditioning stimulus and it is doubtful whether the human limb can be fixed and maintained in a way whereby mechanical tendon stimulation is of comparable intensity from blow to blow.

The exquisite sensitivity of the two-neurone reflex to suppression from within the muscle group activated by it, is indicated in Figure 3. The subject lay prone and as relaxed as possible. Monosynaptic H reflexes of fairly constant size were evoked at regular intervals about every three seconds. Light touch

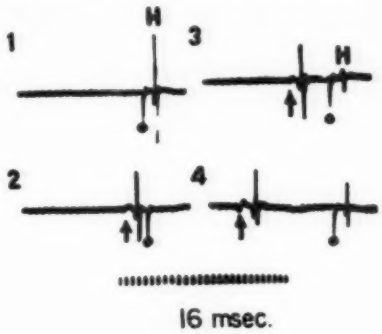

FIGURE 2

Action potentials from calf muscles. Surface electrodes. Record 1—H reflex from submaximal single shock to posterior tibial nerve in popliteal fossa. Records 2, 3 and 4—similar nerve stimulation at intervals of 50, 90 and 200 milliseconds respectively after mechanical tap (indicated by arrow) on Achilles' tendon.

and painful skin stimulation had no demonstrable effect on the magnitude of the reflex response. Likewise, it was unaffected by unpleasant pressure or electrical shocks to Achilles' tendon. A lightest finger tap, however, over the area marked by stripes caused marked reduction or obliteration of the H reflex potential. Heavier blows, over movable adjacent points indicated by crosses, brought forth a similar depression. This was not found when more remote areas or fixed nearby points (circles) were tapped. It seemed as though the effective inhibitory stimulus came from actual jar of the muscle, and, from mere observation, a small portion of it. Faced with these profound suppressive effects from very light mechanical deformation, it was apparent that more delicate and readily-controlled conditioning was necessary.

There is always uncertainty about the receptor organs, or even gross site, from which impulses discharged by electrical stimulation of nerve fibres would

normally have arisen (Lloyd, 1943c). This uncertainty is even greater in human studies where trunks of mixed afferent and motor fibres are of necessity used. The preceding paper has shown that liminal shocks to the posterior tibial nerve activate only the most rapidly-conducting Group I afferent fibres from muscle which subserve the monosynaptic reflex. Slightly stronger stimuli not only increase the size of the Group I volley, but also discharge afferent impulses in Group II fibres. Indeed, the overlap of threshold between the two groups is sufficient that when stimulation intensity is maximal for the synchronous Group I volley, a considerable, though dispersed, Group II bombardment of interneurones occurs. Only, however, with the stronger shocks are antidromic

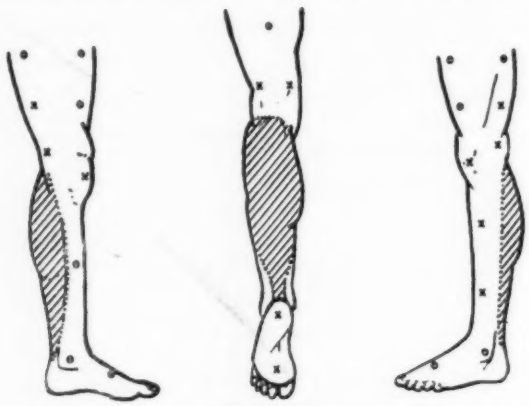

FIGURE 3

Diagram showing where mechanical tap inhibited H reflex in calf muscles evoked by submaximal single shock to posterior tibial nerve in popliteal fossa. Over striped area lightest finger tap suppressed reflex response. Slightly stronger blows over adjacent movable structures (X) had similar effect, but over more remote or fixed points (O) were ineffective. Non-deforming, cutaneous or deep, painful stimuli produced no inhibition.

volleys of slower conduction fired up motor axones. In judging the following experiments, then, it must be remembered that the conditioning effect on motoneurone excitability of preceding liminal stimuli was produced solely by impulses in the lowest-threshold Group I fibres. That caused by only slightly stronger nerve shocks may have been due to increased Group I volleys, but equally well have been caused by afferent impulses in Group II fibres of the same nerve and possibly from the same muscle.

1. Peripheral manifestations

In tracing 8 of Figure 4 the action potentials recorded from calf muscles followed a submaximal shock to the posterior tibial nerve in popliteal fossa.

There was a small motor deflection (M 2) indicating that stimulation was not confined entirely to afferent fibres. The more prominent action potential (H 2) was that of the test reflex. The remaining records illustrate changes in the reflex when it had been conditioned by a preceding similar shock to the same nerve trunk. When the two stimuli were separated by 8 milliseconds (record 1), the test reflex deflection appeared at a corresponding interval after that produced by the conditioning volley. When the interval was increased to 16 milliseconds (record 2), the test response was greatly reduced in amplitude. It was still smaller in record 3 where stimulus separation was 24 milliseconds. At greater intervals up to about 70 milliseconds, no test reflex could be de-

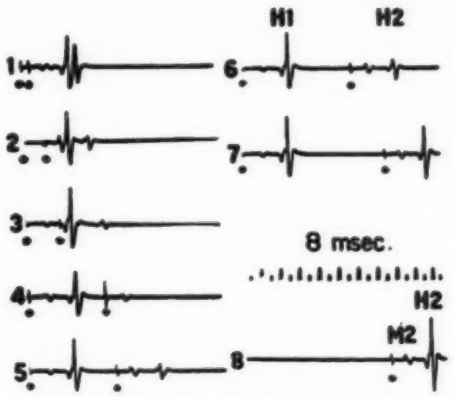

FIGURE 4

Action potentials from calf muscles. Surface electrodes. Single submaximal shock to posterior tibial nerve in popliteal fossa evoked H reflex of record 8. In records 1 to 7, this was preceded by similar conditioning shock at same nerve site at intervals of 8, 16, 24, 64, 72, 88, 120 milliseconds.

tected (record 4). It was apparently completely suppressed. Further separation of nerve volleys (records 5 to 7) permitted some discharge of the test response. Amplitude of the latter more nearly approached its control value as separation became successively greater. Even at an interval of 120 milliseconds, however, (record 7) decreased size indicated that excitability of all motoneurones had not returned to an unconditioned level. This was not reached in most instances for two or three hundred milliseconds.

The records of Figure 4 represented one pattern encountered when the H reflex was so conditioned at different intervals. With increasing separation of the two stimuli, there was a progressive emergence of the test reflex response from depression toward its normal size. In most instances, however, and illustrated by Figure 5, recovery was more complicated. Slow recording was

used to demonstrate these features, so the action potentials have been considerably compressed. Amplitudes, however, may be readily compared. Record 9 shows the H response to a single nerve volley. In the remaining tracings it followed a similar volley which produced the deflection at the beginning of each record. At short intervals (not shown) the test reflex could be detected. In record 1, with stimulus separation of 60 milliseconds, it was completely suppressed. Records 2 and 3, with intervals of 70 and 95 milliseconds respectively, show successively greater recovery in motoneurone excitability. At yet greater stimulation separation (records 4 and 5), amplitude of the test response had not only returned to normal, but was considerably enhanced for a period of time before it returned to its unconditioned size (remaining records). No

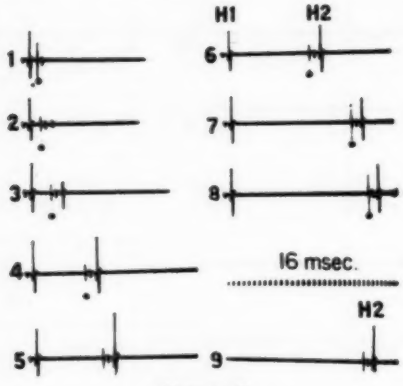

FIGURE 5

Action potentials from calf muscles. Surface electrodes. Single submaximal shock to posterior tibial nerve in popliteal fossa evoked H reflex of record 9. In records 1 to 8, this was preceded by similar conditioning shock at same nerve site at intervals of 60, 70, 95, 190, 240, 380, 440 milliseconds.

explanation has yet been forthcoming for the two differing patterns of recovery in normal persons—in one a progressive return to unconditioned motoneurone excitability; in the other, an interposed phase of enhancement. Similar differences, not completely explained, have also been encountered in other mammals (Eccles and Sherrington, 1930; Granit, 1950) and in frogs (Bremer, Bonnet and Moldaver, 1942).

It should be noted that in the early phases of the recovery period (records 5 and 6 of Fig. 4, and records 3, 4, 5, 6 of Fig. 5), latency of the test reflex was increased beyond its unconditioned value. This additional latency in different experiments has varied from 2 to 8 milliseconds. It has always been greatest in the earliest stages of recovery, and when stimulus interval has been made longer (records 7 of Fig. 4, and 8 of Fig. 5), latency progressively returned

to normal. This may indicate that decreased motoneurone excitability to this direct type of testing was even more prolonged than was superficially apparent, and that reflex discharges during this seemingly early stage of recovery were not, in fact, monosynaptic. In view of the synchronous nature of the testing volley and the length of the delays, it is unlikely that the increased latencies resulted, as Lloyd (1943c) found following stretch, from dispersed arrival at motoneurones of impulses in Group I fibres. It seems more probable that motoneurones, normally discharged by impulses in the most rapidly conducting afferent fibres, and hence unresponsive to those of slower velocity or relayed

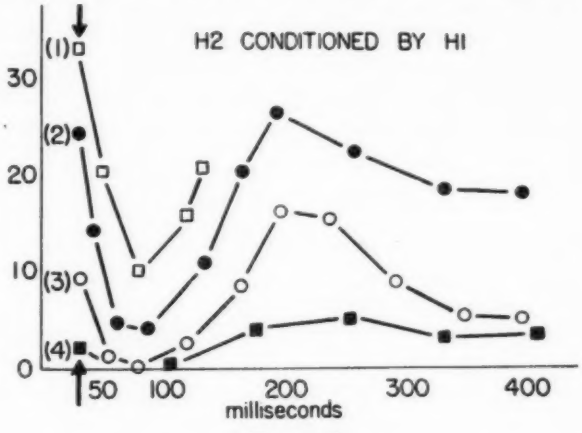

FIGURE 6

Amplitude of H reflex (H 2) after preceding shock, at intervals shown, to same posterior tibial nerve in popliteal fossa. In curves 1 to 4, conditioning nerve stimulus successively increased in intensity. Arrows indicate site of H reflex (H 1) produced by conditioning nerve volley. In this graph, each point represents mean value of many determinations. Ordinate—arbitrary units. Abscissa—time between stimulus producing H 1 and peak of H 2 deflection expressed in milliseconds.

through interneurones in spinal cord, were activated only through these other pathways. This surmise is not, however, susceptible to proof at this time. Similar delays in reflex anterior root discharge were, however, also found in cats by Eccles (1946) during incomplete inhibition produced by strong afferent volleys and likewise attributed to internuncial bombardment of motoneurones.

The H reflex pattern, when conditioned by a preceding shock to the same nerve, was modified by the intensity of the conditioning volley. This is depicted graphically in Figure 6. In this composite diagram the abscissa denotes time in milliseconds after the stimulus artefact of the conditioning volley. Broad arrows, about 32 milliseconds later, indicate the crest of the reflex muscle action potential (H 1) produced by that volley. The ordinate, expressed in

arbitrary units, refers to height of the test reflex response (H 2). The curves show the mean amplitude of the peaks of many test H deflections (H 2) when separated by increasing intervals from the first stimulus. From above downwards, intensity of the conditioning shocks was successively greater, though that of the test stimulus was maintained constant at a strength which produced control H 2 responses of size comparable to the final points of curve 2. It is apparent from the upper curves that impulses in only a few afferent fibres led to a short-lived ensuing period during which a second volley effected some reflex discharge. With greater intervals between stimuli, amplitude of the reflex response was depressed. With successively stronger, but still well submaximal, conditioning shocks which activated more and more afferent fibres, the early phenomenon became progressively less conspicuous, and depression was earlier in onset, more profound, and increased in duration. Indeed, in the lowest two curves, only depression is evident, and that almost immediate in its onset.

2. Spinal root activity

It seems probable that depression of the test reflex when it followed afferent nerve stimulation was associated with a central inhibitory process in some form. This could have been true reflex inhibition or subnormality (Denny-Brown ,1928; Bernhard, 1947; Granit, 1950), or conceivably depression following antidromic impulses in motoneurones (Renshaw, 1941; Eccles, 1946; Bremer, 1947). The latter seemed unlikely as the phenomenon has been encountered when the conditioning volley was of such slight magnitude that it produced little or no evidence of direct peripheral motor activity. Furthermore, the prolonged inhibitory process resembled more closely that found in animals after afferent volleys than the much shorter period of depression which follows antidromic stimulation (Bremer, Bonnet and Moldaver, 1942; Brooks, Downman and Eccles, 1950).

This view was supported by observing depression after stimuli of insufficient intensity to cause any blockage by antidromic volleys of anterior root (A) discharge (Magladery, Porter, Park and Teasdall, 1951). For example, record 2 of Figure 7 shows only the reflex deflection (A 1) evoked by a single submaximal stimulus. Since no dorsal root (R) potential was discernible, the afferent volley was almost certainly confined to Group I fibres (Paper IV of this series). A slightly more intense shock to the same nerve (record 1) produced a similar motoneurone discharge (A 2). When, however, this second stimulus followed the first by 12 milliseconds (record 3), it caused no reflex response. It seems clear, therefore, that the inhibitory process in this instance was not dependent on antidromic activity but attributable to some central effect caused by impulses in low-threshold Group I afferent fibres. Studies of the time course of this depression, as portrayed by anterior root discharge, have not yet been

completed. That it was prolonged is indicated by Figure 8. Again, decreased speed of the cathode ray sweep has considerably compressed the action potentials. It can be seen, however, that the conditioning and test volleys (records 1 and 2) separately evoked clear-cut reflex anterior root discharges (A 1 and A 2) without detectable evidence of antidromic activity. When, however, the

FIGURE 7

Anterior spinal root action potentials reflexly evoked by submaximal shocks to same posterior tibial nerve in popliteal fossa. Records 1 and 2—single nerve volleys. Record 3—double shocks at interval of 12 milliseconds. Amplitude of A deflections about 30 microvolts.

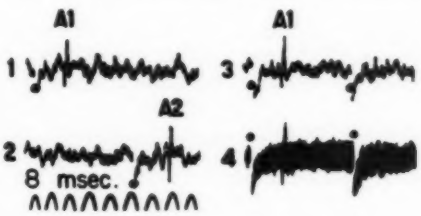

FIGURE 8

Anterior spinal root action potentials reflexly evoked by submaximal shocks to same posterior tibial nerve in popliteal fossa. Records 1 and 2—single nerve volleys. Records 3 and 4—double shocks at interval of 50 milliseconds.

test stimulus followed the conditioning shock (records 3 and 4) by 50 milliseconds, the afferent impulses which it initiated were completely unable to discharge motoneurones.

It is almost self-evident that the depression here described must have been a central process and unrelated to excitability changes in afferent peripheral pathways. This has, however, been put to test by experiments such as that illustrated by Figure 9. The dots mark artefacts produced by two shocks to

the posterior tibial nerve. Record 1 shows that, at an interval of 12 milliseconds and similar stimulus intensities, the second nerve volley evoked no reflex discharge in anterior roots. The deflection (A 1) was produced by the initial conditioning impulses. When the size of the test (second) volley was increased (record 2) the barrage of afferent impulses was sufficiently intense that not only did a small (A 2) reflex discharge occur but also dorsal root action potentials (R 2) were readily detected. Yet greater intensity of the second stimulus (record 3) was followed by increased size of the dorsal root deflection and emergence of the small spike indicative (Magladery, Porter, Park and Teasdall, 1951) of the antidromic volley. This pattern evoked by the stronger test shocks was quite comparable to that normally found without preceding conditioning

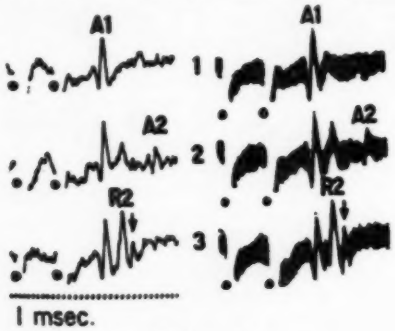

FIGURE 9

Spinal root action potentials. Conditioning and test shocks to same posterior tibial nerve in popliteal fossa at intervals of 12 milliseconds. In records 1, stimuli of equal intensity; reflex response to test volley did not occur. In records 2, increased test volley; small (A2) reflex discharge appeared; dorsal root action potential (R2) of moderate size. In records 3, further increased intensity of test stimulus produced normal R 2 deflection and also antidromic volley in anterior root (marked by arrow).

volleys. It seems clear, therefore, that the inhibitory process was not due in any way to functional alterations caused in afferent peripheral pathways by the conditioning stimulus.

It has also been seen (Figs. 4 and 6) that there was incomplete or no suppression of the test response when stimulus intervals were very short and conditioning volleys weak. Lloyd (1946) and others have, however, demonstrated the onset in cats of an antagonistic inhibitory process well within a millisecond, and its rapid increase to a maximal value. There is no reason to believe that such could not also be the case in man, regardless of its cause. Indeed, early profound depression with stronger conditioning volleys (Fig. 6) shows that such can occur. Emergence, then, of the test deflection at short intervals, and its decay over 15 to 25 milliseconds, must indicate a concomitant central

facilitation whereby motoneurones in the subliminal fringe were activated by the second volley. The actual findings, therefore, as depicted graphically, probably form only a composite expression of simultaneously acting facilitation and depression. With the limitations imposed by the experimental material, it has so far been impossible to separate these processes further. That the interpretation is valid, however, was supported by concurrent studies of spinal root potentials.

In the experiment exemplified by Figure 10, barely subthreshold nerve stimuli were applied peripherally. The first three records show only random

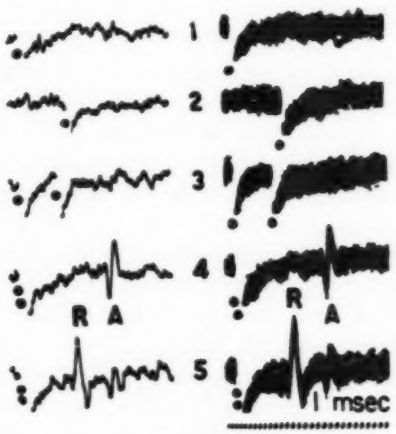

FIGURE 10

Spinal root action potentials evoked by shocks to same posterior tibial nerve in popliteal fossa. Records 1 and 2—similar, just subthreshold, nerve stimuli. Records 3, 4, and 5—these stimuli combined respectively at intervals of 12 and 2 milliseconds, and simultaneously. Note emergence of reflexly-produced anterior root potential (A) at 1–2 millisecond interval. Simultaneous shocks (record 5) merely increased intensity of peripheral stimulus.

activity from intrathecal electrodes when shocks occurred singly, or together at relatively long intervals (12 milliseconds in tracing 3). In record 4, however, stimulus separation amounted only to 1 or 2 milliseconds. Emergence of the anterior root deflection (A) indicates the degree of motoneurone discharge which then occurred. In the final record, in which shocks were simultaneous, the result was merely comparable to that produced by a much stronger single peripheral nerve volley. This experimental limitation made it impossible therefore to discover whether facilitation occurred at intervals less than 1 millisecond.

It seems quite clear then that in man ipsilateral impulses contributing to the lowest threshold myotatic reflexes produce, and the arcs are subject to the

influence of, facilitatory and depressant processes, the composite time course of which has been demonstrated experimentally. Whereas impulses in a few afferent fibres caused an immediate short-lived period during which facilitation was evident, this was followed by a more prolonged phase of predominant depression. With stronger conditioning stimulation, however, no evidence of facilitation was detected—a central inhibitory effect appeared almost immediately and was of greater magnitude and duration. Determination of actual values for the latter was not possible as there was some indication that reflexes obtained during early stages of the recovery phase were not, in fact, monosynaptic.

3. Dorsal spinal cord activity

Due to limitations in intrathecal electrode placement in man, it has only been possible to record slow spinal cord potentials from needles situated dorsal to cord (Magladery, Porter, Park and Teasdall, 1951). Since the after-potentials of motoneurones evoked by antidromic volleys are not recorded by somewhat similar electrodes over dorsum of cord in cats (Gasser and Graham, 1933; Brooks, Downman and Eccles, 1950), it must be emphasized that the deflections which we have recorded were produced by interneurones. They did not, therefore, reflect excitability changes of motoneurones tested by the monosynaptic reflex (Eccles, 1946; Bremer, Bonnet and Moldaver, 1942; Bremer and Bonnet, 1942; Bernhard, 1947; Brooks, Downman and Eccles, 1950). Any alteration produced in these negative and positive spinal internuncial potentials by the afferent volleys described in this communication cannot therefore be attributed to changes in excitability at the final motor synapses. Nevertheless, though produced by impulses in Group II fibres, the potentials have been caused by nerve stimuli which were still submaximal for Group I volleys (preceding paper) and undoubtedly reflect synaptic changes which have considerable functional importance in integrative spinal cord activity. For this reason, and to present a basis for further investigation of this internuncial activity in patients with neurological disease, the intermediary potentials have been recorded under the conditions and tests employed in the earlier sections of this communication (cf. the preceding paper, where the interaction of two maximal afferent volleys in the same nerve trunk was described).

The internuncial action potentials of Figure 11 followed submaximal shocks of approximately equal intensity to the same posterior tibial nerve in popliteal fossa. The critical recording electrode was situated at D 11 vertebral level—that is, dorsal to the lower part of the lumbar enlargement. Stimuli were only sufficiently strong to produce a clearly detectable dorsal root (R) discharge. In record 1, where the stimuli were separated by 36 milliseconds, the deflections caused by the individual nerve volleys were essentially similar. With decrease in interval between shocks, the form and size of the second potential

(records 2 and 3) were little changed. At yet shorter intervals, for example in record 4 where 4 milliseconds separated the stimuli, the deflections were additive. The degree of occlusion may be judged, however, by the relatively smaller contribution by the second nerve volley. In the final record of the figure, showing for comparison the effect of maximal nerve stimulation, the intense nerve volley was achieved by simultaneity of the two stimuli at the periphery.

FIGURE 11

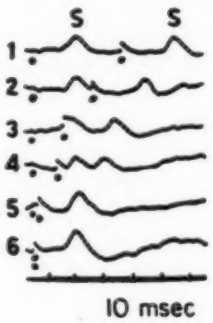

FIGURE 12

FIGURE 11

Intermediary slow potentials recorded from needle electrodes at D 11 vertebral level. Similar submaximal shocks to same posterior tibial nerve in popliteal fossa. In records 1 to 4, stimulus intervals were 36, 18, 7, and 4 milliseconds respectively. In record 5 shocks were simultaneous and volley was merely that of a more intense peripheral stimulus.

FIGURE 12

Intermediary slow potentials recorded from D 11 vertebral level. Conditioning submaximal shock to one posterior tibial nerve in popliteal fossa. Test stimulus was submaximal shock of similar intensity to posterior tibial nerve of opposite leg. In records 1 to 4, stimulus intervals were 32, 22, 13, and 3 milliseconds respectively. In record 5, shocks were simultaneous.

Results were much the same when submaximal volleys reached cord from opposite sides of the body. In Figure 12, for example, the first stimulus was to ipsilateral posterior tibial nerve, and the second to the same nerve of the opposite leg. At short intervals (below 10 milliseconds) and simultaneity, the spinal potentials were additive, again with considerable evidence of occlusion. Due to the fact that different nerve trunks were used, the peripheral summation seen in record 5 of Figure 11 did not occur, and it is quite apparent from tracing 5 of Figure 12 that the central summation applied to both the negative and positive potentials.

In brief then, afferent nerve volleys in man which were followed by facilita-

tion and depression of motoneurone discharge, produced some alteration of interneurone excitability. That there was summation, though with considerable occlusion, was indicated by the additive effect of two volleys at short intervals. During the prolonged period, however, when monosynaptic reflexes were suppressed, no detectable changes were reflected in the intermediary potentials.

DISCUSSION

This investigation was prompted by the variability of reflex responses in man. Whereas painful stimuli to superficial or deep structures of a limb have no apparent effect on a monosynaptic myotatic reflex, the slightest deformation of its muscle may produce profound inhibition. This led to a study of the conditioning effects of weak afferent nerve volleys on two-neurone reflex discharge (Magladery, Porter, Park and Teasdall, 1951). This means of testing motoneurone excitability has been profitably used in animals by Renshaw (1940), Lloyd (1946), Eccles (1946) and others. It soon became apparent that characteristic changes were also caused by afferent nerve volleys in man. It is of particular interest that conditioning effects followed even the weakest of nerve stimuli. Figures 7 and 10 have shown, for example, that both facilitation and depression resulted from afferent volleys which produced no detectable R deflections. The impulses, therefore, were mainly, if not entirely, in Group I fibres (Magladery, Porter, Park and Teasdall, 1951). This deduction is strengthened by the observation that the facilitatory effects were virtually immediate in onset (Fig. 10) with little time available for intervening internuncial activity (cf. Fig. 5 in paper VI of this series). Lloyd (1946) has described comparable facilitation of monosynaptic reflex discharge following Group I afferent volleys in cats. Its immediate onset and time course of decay were quite comparable to those described in this paper. There seems little doubt that the processes were similar and due to the direct convergence on motoneurones of impulses in Group I fibres.

The nature of the inhibitory effect is, however, less clear. It certainly did not result from antidromic impulses in motor axones since the phenomenon occurred (Figs. 7 and 8) when there was no detectable evidence of such impulses. It must, however, be remembered that in these studies some motoneurones were almost invariably discharged by the afferent nerve volleys. It is likely, therefore, that some (at least) of the depression was due to subnormality (Erlanger and Gasser, 1937) following the initial discharge. This interpretation may, in fact, be sufficient to explain the depression seen in curve 1 of Figure 6 which followed the predominant phase of facilitation. When stronger conditioning volleys were used, however, the depression was virtually immediate in onset (Fig. 6) and lasted much longer than that following liminal stimuli. Indeed its true duration is still in doubt and may be even longer than is superficially apparent. Increased latencies, often by several milliseconds, of

the much reduced test reflex responses during early recovery have not been satisfactorily explained in either man or other animals. They may well indicate, as Eccles (1946) suggested, that the reflex discharge was not, in fact, monosynaptic, but due to excitation by interneurones.

Unquestionably many more motoneurones were actually discharged by the strong afferent volleys and the early stages of the depression could well be attributed to motoneurone refractoriness. The long continuance of the inhibitory process, however, needs further explanation. Immunity of the test reflex discharge to depression by painful stimuli, and the painless character of the conditioning shocks, exclude noxious causes (Lloyd, 1946). Clearly, it was more lasting than mere subnormality. A more satisfactory interpretation would be that the depression was produced through internuncial pathways by impulses arising in Group II afferent fibres from muscle. It might well be asked how much of the later stages of the depression was due to autogenetic inhibition, secondarily initiated from the slight muscle contraction of the first reflex response (see Granit, 1950). Certainly this factor cannot be eliminated. Nevertheless it is not necessary to introduce it. Lloyd (1946) has shown that a motoneurone depression occurred in cats when Group II fibres were activated by the conditioning stimulus, and there is little reason to doubt that the phenomena were similar. Furthermore, to anticipate, an equally long-lasting depression following similar volleys from other nerves will be demonstrated in the next paper of this series. It seems probable, then, that the excitability changes in motoneurones which have been described in this communication cannot be attributable to a single cause. On the contrary, the afferent volleys must be considered in terms of the relative contributions made by impulses in Group I and Group II fibres. It seems evident that the early facilitation was due to direct convergence of the former on motoneurones. The prolonged later depression, however, took place when Group II volleys increased in size and caused greater internuncial activity.

It is apparent, however, that only some (and perhaps merely the initial) internuncial activity was reflected in the intermediary potentials recorded from dorsum of spinal cord. Central summation, with marked occlusion, certainly occurred soon after the conditioning volley reached the cord and while facilitation of motoneurone discharge was taking place. It is impossible, at this stage, to assess what, if any, contribution this early internuncial activity made to the actual motoneurone facilitation under these conditions. Probably it was very little, as the facilitation was less evident with the stronger volleys which activated more and more interneurones. Motoneurone depression, on the other hand, became increasingly prominent with stimuli which liberated impulses in successively larger numbers of Group II afferent fibres. This is perhaps understandable when it is noted that no evidence of interneurone depression was found after an initial afferent volley. The effect of the increas-

ingly stronger and dispersed Group II afferent discharge may not therefore have undergone much reduction in the internuncial pathways.

SUMMARY

Motoneurone discharge by a two-neurone reflex has been altered in man by various procedures. Painful stimuli were without influence. Stretch or deformation of the muscle on which the reflex acted, or strong volleys in afferent fibres, produced prolonged depression. Increased latency of reduced test responses during motoneurone recovery suggested that the duration of the inhibitory process was more prolonged than was superficially apparent.

Facilitation was caused by orthodromic afferent impulses in Group I fibres converging directly on motoneurones (Lloyd, 1946). This was found only with weak afferent volleys, and was followed by a period of subnormality. With stronger stimulation, early-appearing and long-lasting suppression of motoneurone excitability ensued. This was not due to antidromic volleys in motor axones. Whereas its early stages may well have been due to motoneurone refractoriness, its persistence likely resulted from interneurone activity produced by afferent impulses in Group II fibres.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

VI. Excitation and Inhibition of Two-Neurone Reflexes by Impulses in Other Nerves[1, 2]

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Discharge of motor impulses to skeletal muscle can be produced and modified through various reflex pathways. Some of these, predominantly myotatic, are direct, and motoneurones are activated through single synapses (Renshaw, 1940; Lloyd, 1943a, 1946; Magladery, Porter, Park and Teasdall, 1951). In most instances, especially evident in the flexor reflexes of animals (Creed, Denny-Brown, Eccles, Liddell and Sherrington, 1932; Lloyd, 1943b) one or more interneurones are interposed between afferent fibre and final common path. Even within the myotatic reflexes, Lloyd (1943c) has found Group II responses and more recently (1950) obtained evidence of a low-threshold polysynaptic arc. Although numerous studies have been made of changes in motoneurone excitability caused by volleys in Group I afferent fibres of low-threshold from muscle, by volleys in purely cutaneous nerves, and by antidromic impulses in motor axones (Renshaw, 1940; Lloyd, 1943b, 1946; Bremer, Bonnet and Moldaver, 1942; Brooks, Downman and Eccles, 1950) little attention has been paid of recent years to the conditioning effects of other types of afferent discharge.

Histological studies in cats have indicated that large afferent nerve fibres from muscle are much fewer in peroneal than in posterior tibial nerves (Rexed and Therman, 1948; Lloyd and Chang, 1948). No information, however, concerning more distal nerve trunks, such as plantar, is available. No comparable human data exist. Electrophysiological studies by Magladery, Porter, Park and Teasdall (1951) have shown that monosynaptic reflexes were readily detected following femoral, sciatic or posterior tibial nerve stimulation. These reflexes were not, however, encountered in anterolateral or small foot muscles following shocks to peroneal or plantar nerves. One possible explanation for the difference might lie in dissimilarities, such as have been mentioned above with cats, between fibre spectra of these different nerve trunks—that, for

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[2] Part of this material was presented to the Association for Research in Nervous and Mental Disease on 15 December 1950.

instance, there may be many fewer of the largest fibres in peroneal and plantar nerves. Another interpretation of the failure to detect monosynaptic reflexes from stimulation of these smaller, and on the whole more distal, nerve trunks has been indirectly suggested by Granit (1950). It may be that central inhibition, for some unexplained reason, always completely prevented monosynaptic discharge to muscles innervated by these nerves. The first speculation has not been put to test histologically. The second is not yet susceptible to challenge in man. In view, however, of the observations, a study has been made of certain conditioning effects of volleys arising in peroneal and plantar nerves.

PROCEDURE

The experimental methods have been described by Magladery, Porter, Park and Teasdall (1951). The peroneal nerve was stimulated through paired needle electrodes in popliteal fossa—impulses in the plantar nerve were similarly discharged behind the ankle. The central effects of such volleys were tested by additional shocks to the same nerves, and by two-neurone reflexes to calf muscles (Magladery, Teasdall, Park and Porter, 1951).

RESULTS AND INTERPRETATIONS

1. Interaction of Two Similar Nerve Volleys

When the plantar nerve was stimulated behind the ankle, or the peroneal nerve in the popliteal fossa, similar action potentials were recorded from small foot or anterolateral muscles respectively. These are illustrated in Figure 1. Intensity of the shocks to the peroneal nerve was progressively increased in records 1 to 4. The initial action potential detected in the anterolateral muscles (M) was produced by efferent impulses in motor axones. This deflection became successively greater, up to a maximal size, as stimulus strength was increased. Following the stronger shocks, after a latency of 38 milliseconds, a smaller, variable potential change was detectable. It followed some stimuli—there was no trace of it after others. It tended, for the most part, to increase in size with increasing strength of nerve stimulation. Its latency, however, was inconstant. This second potential was described by Magladery and McDougal (1950). On the strength of latency differences and relative sensitivities to anoxia of different nerve fibres, its reflex nature was recognized. For descriptive purposes, it was designated as the F reflex. Lack of obliteration with even the strongest nerve volleys (cf. the monosynaptic reflex) showed that its afferent impulses travelled mainly, or exclusively, in fibres other than those of the highest velocity, or that its central delay was longer.

Little or nothing is known of the functional significance of the F reflex. Further distinction, however, from the monosynaptic reflex has been seen when an initial shock to either peroneal or plantar nerve was followed by a similar stimulus at various intervals. The results of such an experiment are

illustrated in records 5 to 7 of Figure 1. It is apparent that the F reflex of the second volley (F 2), though variable, was not obliterated regardless of its interval after the first afferent volley (to compare the dissimilar findings with H reflexes, see Figure 4 of paper V in this series). This persistence of F deflections after a conditioning stimulus, has been consistently found and has come to be recognized as an additional feature in differentiating these responses from H reflexes.

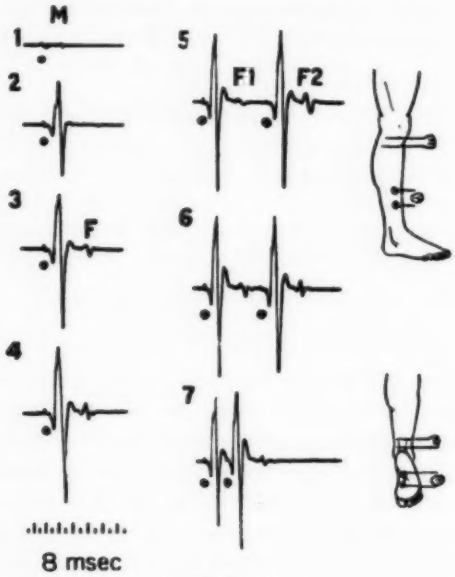

FIGURE 1

Action potentials from anterolateral muscles. Left-hand column—single shocks of increasing intensity through needle electrodes to peroneal nerve. Right hand column—double peroneal nerve shocks, of intensity similar to that producing record 4, at intervals of 80, 70, and 30 milliseconds, respectively.

Apparently then, whatever the mechanism, F reflexes were neither blocked by single antidromic volleys nor were they obliterated by afferent impulses (hereafter referred to as F volleys) produced by strong preceding stimuli to the same nerve. These dissimilarities to monosynaptic reflexes have not been explained by spinal recording. Magladery, Porter, Park and Teasdall (1951) have already pointed out that strong F volleys have not produced sufficiently synchronous dorsal root discharge to enable detection. Nor have anterior root reflex responses been recorded following such stimuli. By contrast, however, it was shown that typical slow potentials were produced in interneurones. Since antidromic volleys do not produce internuncial potentials (Gasser and Graham,

1933; Brooks, Downman and Eccles, 1950), it can be seen that the F volleys did activate secondary neurones in spinal cord. This is not in any way, however, to state that F reflexes are polysynaptic through interneurones. That correlation has not yet been made. It does indicate, however, the internuncial route through which F volleys might alter motoneurone excitability.

2. Effect on Motoneurone Excitability of F Volleys

Despite failure to alter perceptibly one F reflex discharge by a preceding volley in the same nerve trunk, F volleys did affect motoneurone discharge when it was tested otherwise. The method, originally proposed by Renshaw (1940), has already been used (Magladery, Teasdall, Park and Porter, 1951) to study central effects of afferent impulses in nerves which did show detectable Group I fibre activity. The monosynaptic (H) reflex to calf muscles tests

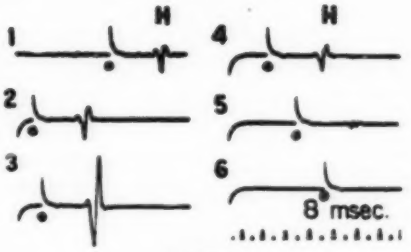

FIGURE 2

Action potentials from calf muscles. Record 1—H reflex from single submaximal shock to posterior tibial nerve in popliteal fossa. In remaining records, this followed, at intervals of 12, 16, 32, 50, and 70 milliseconds, stimulus to plantar nerve behind ankle. Plantar nerve shock indicated by dip at beginning of tracings.

motoneurone excitability (to this form of excitation, at any rate) in its cord segment. In the present investigations, it was preceded, at different intervals, by F volleys in peroneal or plantar nerves. In spite of the most careful placement of stimulating needle electrodes, limitation of shocks in the popliteal fossa to peroneal nerve alone was difficult and uncertain. In most instances, therefore, the conditioning volley was discharged from the plantar nerve behind the ankle. This had a further advantage in that the foot muscles which it innervated were synergists of the calf muscles from which the test reflex response was recorded (Lloyd, 1943b) and thereby antagonistic effects were avoided.

Figure 2 illustrates the results obtained when the monosynaptic reflex was tested after stimulation of the plantar nerve. Record 1 shows the muscle action potential of the test H reflex alone. In the succeeding records, the stimulus artefacts of the conditioning shocks behind the ankle were dips at the beginning of each tracing. Dots mark artefacts of the stimuli which produced the

test reflex. When the shocks were separated by 12 milliseconds (record 2) the H deflection was of normal size. In record 3, the test stimulus was applied 16 milliseconds after the first. It is apparent that the two-neurone reflex was considerably greater than in record 1. This period of enhancement was, however, short-lived. Later records of the figure show the decay and then suppression of the test reflex at greater intervals.

Recovery with further stimulus separation is not shown in Figure 2. The records of Figure 3 were taken from the same experiment, but at slower sweep speed to illustrate this recovery. An early enhancement of the test response at the 16 millisecond interval is apparent in record 2. With 72 milliseconds separation (record 3) the H reflex was much reduced in size. One hundred and twenty milliseconds after the conditioning shock, the afferent test volley was more effective but still considerable depression was evident. Only at intervals

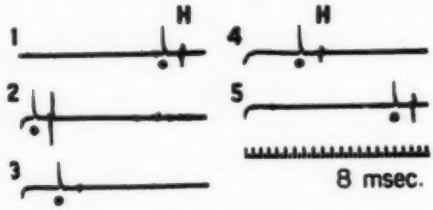

FIGURE 3

Similar to Figure 2 but at slower sweep speed. In records 2 to 5, test shock followed plantar nerve stimulus by 16, 72, 120, and 260 milliseconds respectively.

of 200 or more milliseconds was the monosynaptic reflex unaffected by a preceding F volley.

These figures have shown that conditioning by impulses arising in the plantar nerve produced first facilitation and then depression of motoneurones whose axones innervated synergistic muscles. The sequence was similar to that previously demonstrated with impulses in posterior tibial nerve. The similarity between the two effects was seen, however, to be limited when the intensity of the conditioning stimulus was altered. This is shown graphically in Figure 4 which may be compared with Figure 6 of the preceding paper (Magladery, Teasdall, Park and Porter, 1951). The abscissa indicates time in milliseconds after the artefact of the stimulus to the plantar nerve which produced the F volley. The ordinate, expressed in arbitrary units, shows the height of the test reflex response (H). Each point represents the mean amplitude of the peaks of many test deflections when separated by increasing intervals from the first stimulus. With weak plantar nerve shocks, hardly perceptible to the subject, an evident facilitation occurred—size of the monosynaptic response was enhanced. This potentiation reached its peak about 50 milliseconds after the

conditioning stimulus, or (allowing for reflex time and duration of the muscle action potential) excitability of the tested motoneurones was at its height about 28 milliseconds after the shock at ankle. This then gradually returned to normal. With stronger conditioning stimuli, and hence activation of more afferent fibres, facilitation increased but was then followed by a prolonged period when the test reflex was diminished. With strongest (though not painful) shocks, early preponderance of facilitation was even more marked (closed circles of figure). It gradually decayed over a period of about 20 milliseconds. Subsequent depression in amplitude of the test deflection then followed a temporal course comparable to that described previously. It has already been shown by Mag-

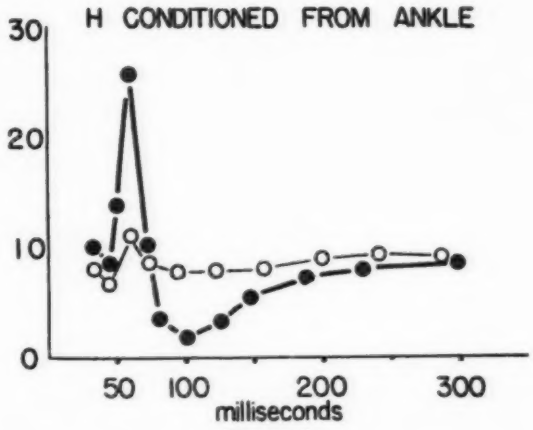

FIGURE 4

Amplitude of H reflex (H) after preceding shock, at intervals shown, to plantar nerve behind ankle. Conditioning (plantar) stimulus greater in curve of closed circles than in other. Each point represents mean value of many determinations. Abscissa—time in milliseconds of peak of H reflex after shock to plantar nerve. Ordinate—arbitrary units.

ladery, Teasdall, Park and Porter (1951) that when monosynaptic reflex discharge was conditioned by a preceding volley of Group I low-threshold afferent impulses, facilitation was only demonstrated when the first volley was weak. With stronger volleys, and hence activation of Group II fibres as well, only inhibitory effects were detected. In contrast, the present experiments have shown that F volleys caused a marked increase in excitability of the same motoneurones, which became greater with increasing size of the nerve volleys.

Another dissimilarity between the central effects of afferent volleys in the two nerves was found when the time course of the intermediary (interneurone) potentials produced by each was compared with that of the facilitation of motoneurone discharge. These have been plotted diagrammatically in Figure

5. The solid lines of graphs 1 and 2 are reproductions of the internuncial potentials (see also Fig. 11 of Magladery, Porter, Park and Teasdall, 1951). Latency from plantar nerve stimulation behind the ankle (graph 1) was 20 milliseconds; from the posterior tibial nerve in popliteal fossa (graph 2) it was 11 milliseconds. Only the difference, 9 milliseconds, therefore, can be allowed for conduction of F volleys from ankle to popliteal fossa. Thus, when a test volley from the posterior tibial nerve was discharged 9 milliseconds after a

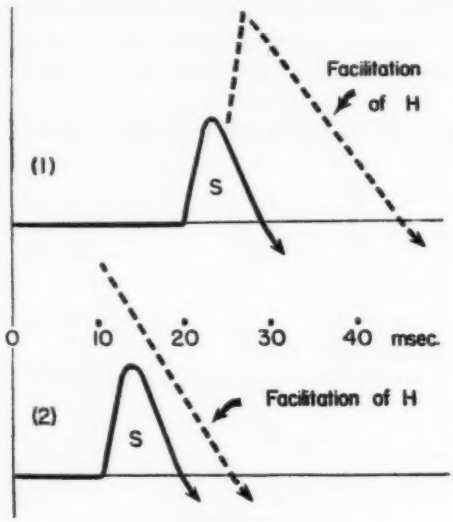

FIGURE 5

Curves of facilitation (broken lines) produced by, (1) afferent F volleys from plantar nerve stimulation, and (2) low-threshold afferent impulses from posterior tibial nerve. These have been matched in time with direct tracings (solid lines) of internuncial spinal cord action potentials produced by stimulation at the two sites. Time intervals in milliseconds.

In graph 2, facilitation was immediate in onset, preceding the internuncial activity. In graph 1, facilitation developed only after considerable internuncial discharge had occurred. See text.

conditioning F volley from the plantar nerve, the afferent impulses from each stimulus reached the spinal cord simultaneously. Likewise when the plantar nerve was stimulated 12 milliseconds before the posterior tibial, the F volley arrived centrally 3 milliseconds before the impulses of the test volley.

The broken lines of Figure 5 indicate the different patterns of facilitation produced by F volleys (graph 1), and by Group I low-threshold afferent impulses from posterior tibial nerve stimulation (graph 2). It can be seen from graph 2 (data taken from Figures 6 and 10 of Magladery, Teasdall, Park and Porter, 1951), that when the conditioning volley was from the posterior tibial

nerve, facilitation was immediate in onset. Its peak occurred before the internuncial potentials had developed. It then decayed over about 15 milliseconds. Were the central mechanisms similar, it would be expected that the facilitation produced by F volleys from plantar nerve would follow an identical time course. This has not been found to be the case (graph 1). Even when conditioning F volleys from plantar nerve reached the spinal cord 3 milliseconds before the test volley (record 2 of Figure 2), no facilitation occurred. Only, in fact, when motoneurones were tested by a monosynaptic reflex 7 milliseconds after the arrival of F volleys at spinal cord, was marked enhancement of excitability found (record 3 of Fig. 2). By this time, as reflected in the slow action potentials, considerable internuncial activity had developed. This relationship can be seen from graph 1, wherein the peak of the facilitation curve occurred well after the crest of the negative internuncial potential. The exact time of onset of the facilitatory process has not yet been determined. Its beginning has, therefore, been left open in graph 1. It can only be stated that it started somewhere between 3 and 7 milliseconds after the F volley reached spinal cord. In brief, then, low-threshold afferent impulses from muscle in posterior tibial nerve caused immediate facilitation of motoneurone discharge. F volleys from plantar nerve, in contrast, increased motoneurone excitability only after a delay of several milliseconds during which the negative internuncial action potential made its appearance.

DISCUSSION

The contrasting effects of increased stimulus intensity on monosynaptic H reflexes, and on the F reflexes evoked in anterolateral and calf muscles, suggest that most afferent fibres contributing to these responses were physiologically different. Since the afferent limb of the monosynaptic arc is composed of the lowest-threshold Group I fibres from muscle, it seems evident that these were not responsible for the F reflexes. Painful stimuli to skin and deep structures do not modify a monosynaptic test reflex (Magladery, Teasdall, Park and Porter, 1951). Marked motoneurone inhibition has, however, followed stimulation of the plantar nerve (Figs. 2, 3, and 4 of the present paper). By exclusion, therefore, it may be reasoned that afferent impulses which led to F reflex production did not subserve pain perception. Fibres leading from other receptor endings such as those in periosteum or joint surfaces may have been responsible, but it is more likely that the impulses travelled centrally in pathways, other than Group I, from muscle or tendon. This question of source must, however, be left in abeyance. There is no evidence, either from these experiments or from animal studies, pointing one way or the other.

It is of interest to compare the dissimilar conditioning effects on monosynaptic reflex discharge of afferent volleys in Group I fibres of low-threshold (Magladery, Teasdall, Park and Porter, 1951), and those F volleys of higher threshold

from plantar nerve which have been described in the present paper. In the former, the weakest of volleys led to facilitation. With stronger stimulation, only depression, probably associated with motoneurone refractoriness and inhibition produced by Group II impulses, ensued. F volleys were, on the other hand, followed by increasingly greater and more long-lasting facilitation of motoneurone discharge when the stimuli were made stronger. Furthermore, the facilitation caused by these impulses of higher threshold (Figs. 4 and 5) rose progressively to a peak and then gradually declined. It may be compared with that found with low-threshold impulses where maximal facilitation was immediate (Fig. 5, and also Fig. 6 of Magladery, Teasdall, Park and Porter, 1951). These differences may indicate different loci for the conditioning influences of the two types of nerve volley. Since that of Group I impulses is almost certainly directly at motoneurones (Lloyd, 1946; Eccles, 1946; Bremer, Bonnet and Moldaver, 1942) it seems probable that F volleys affected motoneurone excitability only through more complex central pathways.

This interpretation is substantiated by close examination of the temporal course of the facilitatory effects caused by the two volleys (Fig. 5). Those afferent impulses of low threshold, produced in Group I fibres by submaximal stimulation of the posterior tibial nerve, increased motoneurone excitability immediately on reaching spinal cord. On the contrary, there was a lapse of several milliseconds after F volleys first reached interneurones before facilitation at motor nerve cells occurred. Delays of such magnitude almost certainly indicate the interposition of several interneurones (Lorente de Nó, 1938; Lloyd, 1943a). This suggests the pathways through which the facilitation described in this communication was produced.

The means, however, whereby suppression of motoneurone excitability occurred after the prolonged facilitation, is not clear. Since the motoneurones were discharged for the first time by the test monosynaptic reflex, it is apparent that refractoriness and subnormality of motor nerve cells were not involved. An inhibition of the motoneurones by antidromic impulses in adjacent motor nerve cells (Renshaw, 1941) cannot be ruled out. Certainly the stimuli at the ankle were intense enough to activate many motor axones. If, however, this is the correct explanation, the depression so produced must have been one readily overcome initially by facilitation (Fig. 4), and there is no precedent from animal experiments for such. It is more probable, therefore, that the inhibition was caused by the afferent F volleys and their relay through internuncial neurones. This explanation has, moreover, support from similar studies in cats (Lloyd, 1946).

This is the second situation, then, in which marked motoneurone depression has appeared following internuncial discharge by afferent volleys. In the first case (Magladery, Teasdall, Park and Porter, 1951), it occurred after discharge of afferent Group II impulses in the nerve which supplied the calf muscles.

In the present instance, it was caused by stimulation of a nerve which innervated muscles synergistic to those calf muscles. In both, interneurones were activated and, although causal relationship was not established, provided a possible central pathway through which the depressant effect might well be mediated. Internuncial activity seemed, indeed, to be the only common factor in the two instances.

Facilitation, on the other hand, has appeared in two ways. It has been found immediate in onset following arrival at motoneurones of impulses in afferent Group I fibres from calf muscles. Facilitation in this instance was perhaps analogous to that which Granit (1950) obtained in cats with slight stretch of the involved muscle. He speculatively assigned to it the role of "speeding up" a weak contraction. The facilitation described in the present paper, however, was caused by afferent volleys in a nerve which supplied synergistic muscles. The process was much slower in onset due to the intermediary of interneurones, but became increasingly more prominent as size of the afferent volleys increased. It might be that this offers an important means whereby fixation of the ankle, so necessary to effective function of small foot muscles, is initiated.

SUMMARY

In contrast to the ready production of monosynaptic reflexes in man by stimulation of low-threshold afferent fibres in femoral, sciatic, and posterior tibial nerves, only F reflexes (Magladery and McDougal, 1950) have been detected following strong stimuli to peroneal and plantar nerves. Afferent F volleys in plantar nerves were of high threshold and too dispersed for detection at dorsal roots. They produced, however, prominent slow potentials in interneurones of spinal cord.

Motoneurone excitability, as tested by a two-neurone reflex, was altered by a preceding F volley. Facilitation increased with size of the conditioning volley, and was of greater duration than when it was produced by Group I volleys in posterior tibial nerves. From latency determinations, it was shown that these conditioning effects arose through the intermediary of interneurones. A possible role of these differing facilitatory processes in synergistic function has been suggested.

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ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN

VII. Certain Effects of Brief Stretch[1, 2]

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In the preceding papers of this series it was shown that motoneurone excitability, as tested by a monosynaptic reflex, was altered by preceding afferent volleys produced electrically both in fibres of low and of higher threshold. Profound depression was also caused by gross stretch or deformation of muscle, though the methods of producing it were not adequate for detailed investigation. No facilitation was, however, at any time observed. Lloyd (1943) has shown that in cats the most prominent at least of the myotatic reflexes are subserved by afferent Group I fibres. Since impulses in those fibres have produced only facilitation directly at their corresponding motoneurones (Lloyd, 1946), it might have been expected that brief stretch in man, if producing myotatic effects only through Group I fibres, would also have been followed by enhancement of motoneurone excitability. The finding, therefore, solely of depression, despite these crude methods of stretch, raises a question whether or not other groups of afferent fibres from muscle, activated by this means, alter motoneurone discharge. Similar long-lasting inhibition of monosynaptic reflexes in cats was found by Granit (1950) secondary to vigorous stretch or contraction of the muscle to which they led. The profound depression is also remindful of that encountered in man with all but the weakest of posterior tibial nerve volleys (Magladery, Teasdall, Park and Porter, 1951) which certainly contained numerous impulses in Group II fibres. There has been, however, no demonstration of naturally-produced conditioning effects exerted by afferent impulses from muscle in these Group II fibres. The present experiments were undertaken, therefore, to study more closely the effects of brief stretch of muscle on motoneurone excitability, and more especially to look for any evidence of alteration due to afferent impulses in fibres other than those of Group I.

In experimental animals (Creed, Denny-Brown, Eccles, Liddell and Sherrington, 1932; Lloyd, 1943; Granit, 1950) it is possible to produce stretch in a soli-

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[2] Part of this material was presented to the Association for Research in Nervous and Mental Disease on 15 December 1950.

tary muscle fairly discretely, and isolate its influence from that of other possible conditioning sources. In intact man, however, it is impossible to introduce that factor alone without concomitant stimulation of skin and deeper structures, and alteration of tension in muscles other than those under investigation. The possibility, therefore, of making rigidly controlled studies of the effects of brief stretch are of necessity limited. Nevertheless certain similarities of the results of stretch to those obtained from electrical stimulation of nerve trunks have become apparent.

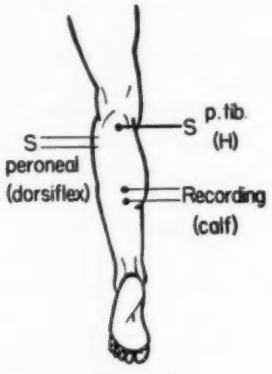

FIGURE 1

Experimental arrangement for study of stretch. Strong peroneal nerve stimulation (S) caused brisk dorsiflexion of foot and sudden stretch of calf muscles. Action potentials recorded from surface electrodes. Testing monosynaptic reflex evoked from submaximal posterior tibial nerve shocks (S).

PROCEDURE

The general methods of stimulation and recording have been described by Magladery, Porter, Park and Teasdall (1951). Additions to the procedure are indicated in Figure 1. Brief stretch of calf muscles was produced by the dorsiflexion resulting from strong single shocks, through paired needles, to the peroneal nerve in popliteal fossa. It must be emphasized therefore that the term "brief" is only a relative one. Certainly, for example, the stretches were much more prolonged than those employed by Lloyd (1943), though less different from those used by Granit (1950). Essentially similar stretch occurred in quadriceps when the sciatic nerve was excited, and in hamstrings when the femoral nerve was the site of stimulation. Muscular contractions produced by shocks to other main nerve trunks in the lower extremity did not cause sufficient stretch of antagonists to be used. Since the excursions of the leg with contraction of quadriceps and hamstring were very wide, and movement of recording electrodes inevitable, studies were mainly confined to stretch of calf muscles (Fig. 1).

It was recognized that the method was unavoidably limited by central effects produced by afferent impulses initiated in the stimulated nerve itself. To some extent this factor was controlled by attributing to stretch only those effects which could be obliterated by gripping the limb and thus reducing movement to a minimum. Motoneurone excitability was tested,

as described previously, by monosynaptic (H) reflexes to calf muscles evoked by submaximal stimulation of the posterior tibial nerve in popliteal fossa (Fig. 1).

Most of the experiments described in this communication were made on normal adults of different age groups. In some instances, as indicated in the body of the paper, patients with clinically absent "tendon jerks" were used.

RESULTS AND INTERPRETATIONS

Strong single stimuli to the peroneal nerve produced rapid and ample dorsiflexion at the ankle, thereby stretching calf muscles. With close observation, sudden arrest could usually be detected towards the end of the movement, as though it had been checked in some way. A characteristic pattern of action potentials was recorded from the electrodes overlying those muscles (Fig. 2).

FIGURE 2

Action potentials from calf muscles. Single strong shocks to peroneal nerve to induce brisk dorsiflexion of foot. P—muscle deflections spread from anterolateral muscles. C—reflex response to stretch in calf muscles. Record 1—free movement. Record 2—foot held by observer.

The stimulus artefact, marked by a dot, was soon followed by a deflection which is labelled in these, and subsequent, records as P. It was similar in configuration and latency to the much larger potentials detected over the contracting anterolateral muscles, and identified as spread from that region. In record 1, some 65 milliseconds after nerve stimulation, an outburst of action potentials appeared in the calf muscles. In this particular experiment, which was typical of most, it was repetitive and consisted of a series of spikes continuing for about 35 milliseconds. In a few cases it was more highly organized and made up of fewer components or even a solitary spike. The electrical outburst has been designated for descriptive purposes as the *C response*. It has been found to date in calf muscles of all normal persons, provided that discrete and effective peroneal stimulation was possible. Only occasionally has its amplitude been sufficient to appear as spread in records from electrodes placed over anterolateral muscles. In one individual, perhaps because of anatomical differences, excitation of the posterior tibial nerve could not be avoided, monosynaptic reflexes appeared, and no C response was obtained (see later).

The second record of Figure 2 shows the result obtained when the foot was gripped firmly by an observer, and thus stretch of calf muscles largely pre-

vented. There was very little C response. Mere manual pressure on the foot, or painful stimuli to skin and deeper structures, introduced no alteration as long as movement was permitted to take place. This relationship, taken in conjunction with latency, served to identify C deflections with reflex responses to rapid stretch of the calf muscles. They apparently represented asynchronous motor discharges in response to successive bombardment of different groups of motoneurones over at least 35 milliseconds. This prolonged discharge may have been due to progressive recruitment of activity in more and more stretch receptors, or equally well have represented motoneurone discharge in succes-

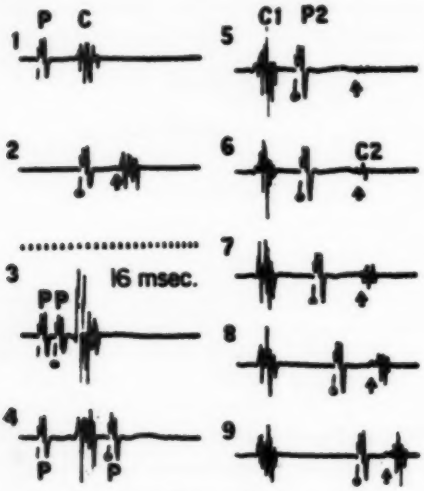

FIGURE 3

Action potentials from calf muscles. Shocks to peroneal nerve to induce brisk dorsiflexion of foot. Records 1 and 2—single shocks. In remaining records, test stimulus (indicated by dot) applied at successively greater intervals after first shock. See text.

sion by a variety of reflex mechanisms of differing time course, and possibly number of synapses (see previous papers of this series).

1. Depression after stretch

After a C response in calf muscles had been evoked in this fashion, a second peroneal nerve stimulus within 100 to 200 milliseconds failed to set up a similar response. Duration of the ineffective period varied with intensity of the initial stretch and also, to some degree, from individual to individual. Figure 3 was, however, illustrative of most such experiments. Dots indicate artefacts of the second peroneal nerve stimuli—arrows, the beginning of the second C response when present. Records 1 and 2 were produced by the two nerve stimuli in-

dependently. The remaining tracings show the responses of the two shocks when separated by various intervals. In the records of the right hand column, initial P deflections were not, for economy of space, shown on the tracings. The first deflections were those of the C response induced by the first stretch. Record 4 shows that the second stretch was ineffective when it followed the first by 120 milliseconds. When, as in records 5, 6, and 7, the intervals were successively longer (about 140, 160, and 190 milliseconds, respectively), C responses (C 2) were produced by the second stretch. Their latencies were all increased over the normal value (see record 2). It can be seen, however, that the delay in appearance was similar in all three records. It must therefore have been related, not only to the second stimulus but more to the time interval after the first stretch. In record 8, however, where a more usual C response was produced by the second stretch, latency was seen to be truly increased by several milliseconds, and only returned to normal in the last tracing. Such being the case, it seems likely that part of the more evident delay at shorter intervals (record 6, for example) was also due to the same cause. Increased reflex latency has been encountered previously during the early recovery period of a conditioned H reflex (Magladery, Teasdall, Park and Porter, 1951). In that case, it was suggested that this indicated more delayed reflex mechanisms. A similar process may well be operative here. In this instance, however, it must be pointed out that continuing discharge of receptor organs might still have been taking place, and that the delay may actually have occurred at the motoneurone (Lloyd, 1943).

With these irregular asynchronous action potentials spread over so many milliseconds, it has not been possible to identify with any certainty evidence of facilitation at short intervals. This is not in any sense to disclaim its occurrence under these conditions. It seems likely that here, as has already been shown to be the case with other interactions, strength of the first stimulus (stretch) has always been sufficiently great that only inhibitory effects have been detected. In this regard, however, record 3 of Figure 3 is of interest. With the 32 millisecond stimulus interval, the second C response was completely obliterated. Amplitude of the C deflections produced by the first stretch, on the other hand, was strikingly enhanced. This potentiation, occurring before afferent impulses discharged by the second stretch could possibly have reached spinal cord, must indicate a facilitatory action caused by afferent volleys produced in the peroneal nerve by the second shock. Similar early facilitation of a monosynaptic reflex response by strong afferent F volleys was found by Teasdall, Park, Porter and Magladery (1951). In these two instances then, the afferent impulses discharged by the conditioning and test stretches showed features remindful, respectively, of electrically-produced afferent volleys in Group II and in Group I fibres. The profound depression following the initial stretch strongly resembled that caused by Group II volleys from posterior tibial nerve

stimuli of moderate intensity (Magladery, Teasdall, Park and Porter, 1951). On the other hand, facilitation following F volleys, as seen in record 3 of Figure 3, has regularly been encountered with test monosynaptic reflexes of which the afferent limbs were Group I fibres (Teasdall, Park, Porter and Magladery, 1951).

2. Facilitation and depression associated with stretch

To study more carefully the processes indicated above, motoneurone excitability was tested by monosynaptic reflexes at various intervals during and after stretch. Conversely, the conditioning effects of these submaximal posterior tibial nerve volleys on subsequent stretch responses was determined by earlier placement of the former.

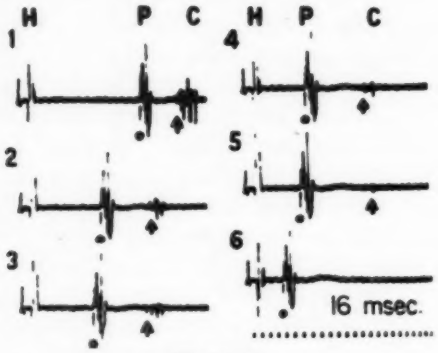

FIGURE 4

Action potentials from calf muscles. Stretch-producing shocks to peroneal nerve (marked by dots) at successively decreasing intervals after submaximal shocks to posterior tibial nerve. See text.

When stretch was produced soon after posterior tibial stimulation, its reflex response (C) was always suppressed. No evidence of facilitation was detected even at the shortest intervals. The total duration of the suppression was to some extent dependent on the intensity of the conditioning nerve stimulus but was usually no longer than 200 milliseconds. Figure 4 illustrates an experiment showing this relationship. Muscle action potentials of the monosynaptic (H) reflex are at the left of each tracing. Dots mark each stretch-producing peroneal nerve stimulus. In record 1, separation was sufficiently great (280 milliseconds) that the stretch response (C) was virtually normal. At shorter intervals (record 2) its latency was increased by several milliseconds. In records 3, 4, and 5, in which the stretch was evoked still earlier after the posterior tibial nerve stimulus, the C response was yet further delayed and successively decreased in size. Furthermore, as was already noted in the inter-

action between two stretches, the delays in records 3, 4, and 5 were identical. They were, therefore, related not entirely to the stretch but to the conditioning volley as well. Apparently under these conditions either the depression produced by the conditioning impulses allowed only the last of asynchronous afferent volleys from muscle receptors to discharge motoneurones, or the motoneurones were activated through more delayed pathways.

When monosynaptic reflexes were used to test motoneurone excitability at different intervals after stretch, not entirely consistent results were obtained. Rather, the conditioning effect in different subjects fell into one of two patterns for which there is no completely satisfactory explanation. The first pattern is

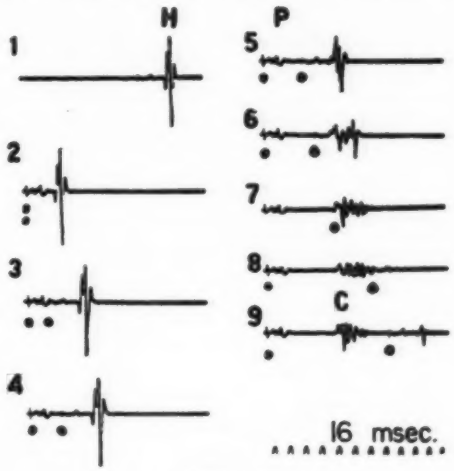

FIGURE 5

Action potentials from calf muscles. Record 1—control monosynaptic test reflex (H). Remaining records—test reflex (indicated by second dot) at successively greater intervals after peroneal nerve shock producing stretch of calf muscles. See text.

illustrated by Figure 5. Record 1 shows the monosynaptic reflex alone. In the remaining records, it followed the stretch-producing peroneal nerve stimulus by increasing intervals. It is apparent, with stimulus separation up to 120 milliseconds (record 8), that either the test reflex completely inhibited the response to stretch, or the converse took place, dependent on which occurred first. The pattern was one solely of depression.

More commonly, however, the conditioning effect of stretch was more complex. This is illustrated in the records of Figure 6. The action potential of the test monosynaptic (H) reflex is shown in record 9. When this fell, as indicated in records 1 to 3, just before, and during a stretch response, its amplitude was markedly increased far beyond its normal value. This appears to represent

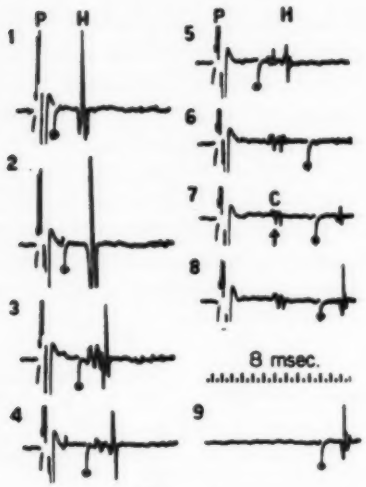

FIGURE 6

Similar to Figure 5. Different experimental subject. See text.

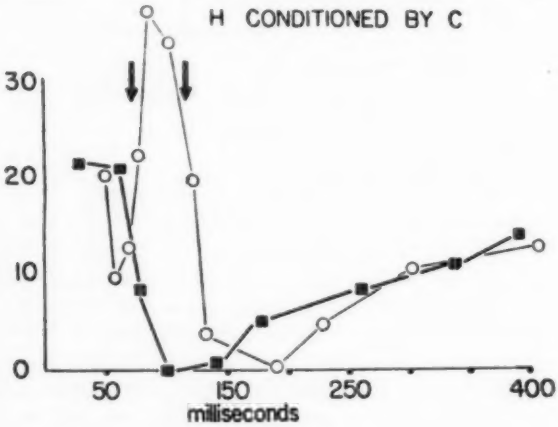

FIGURE 7

Amplitude of monosynaptic (H) reflex response following preceding shock, at intervals shown, to peroneal nerve producing stretch of calf muscles. Most common pattern indicated by open circles. Curve of solid squares less frequently found. Ordinate—arbitrary units. Abscissa—time in milliseconds. See text.

dominant facilitation. Emergence of the usual inhibitory pattern was evident in the later records of the figure. The two different patterns have been plotted from data of representative experiments in Figure 7, and the differences can be readily seen—strong facilitation in one; only depression in the other.

3. Relation of two-neurone arcs to brief stretch

Importance of the two-neurone arc in myotatic responses to brief stretch in cats has been pointed out by Lloyd (1943). In the present experiments, likewise, there has also been evidence, mainly by analogy, that monosynaptic reflexes contribute to C responses. The latter, for example, showed facilitation when conditioned by F volleys in the same fashion as monosynaptic reflexes do (record 3 of Figure 3). Furthermore the facilitation of a test reflex during the early stages of stretch, when afferent discharge had not reached its peak, strongly resembles the conditioning effects produced by impulses in Group I fibres (Magladery, Teasdall, Park and Porter, 1951). There was also, however,

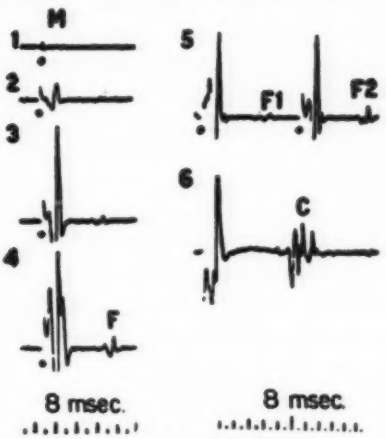

FIGURE 8

Action potentials from calf muscles of person with no ankle jerks, but apparently normal function. Records 1 to 4—single shocks of increasing intensity to posterior tibial nerve in popliteal fossa. Record 5—double similar shocks at 100 millisecond interval. Record 6—shock to peroneal nerve inducing brisk stretch of calf muscles. See text.

strong indication that more complex reflex arcs were involved in these myotatic reflexes as well. Lloyd (1950) has already indicated this possibility in cats. Certain of the present observations, too, are difficult to explain on any basis other than the presence of reflexes additional to those of a single synapse. Increased latencies of C responses during the early stages of recovery from depression may be due to delay in more complex arcs. More striking, however, has been the profound motoneurone depression following stretch. Such markedly lowered reflex excitability has not been encountered in man following impulses discharged solely in Group I fibres. Finally, there is good reason to believe that "tendon jerks" depend largely on monosynaptic reflexes. It is well recognized that absence of those tendon responses is not incompatible with good

function and therefore it is difficult to believe that myotatic reflexes do not exist in some form under those circumstances. It has accordingly been of interest to study the responses to brief muscle stretch in people who, because of age or previous disease, had no detectable "ankle jerks."

Figure 8, for example, illustrates action potentials from calf muscles in a man who had apparently recovered completely from a peripheral neuritis. His "ankle jerks", however, remained absent. As shown in the records of the left hand column, weak electrical shocks to his posterior tibial nerve produced no monosynaptic low-threshold reflex responses in his calf muscles. On the contrary, and only with much stronger stimuli, small variable deflections appeared. That these were similar to F reflexes (Teasdall, Park, Porter and Magladery, 1951) was established in record 5 wherein a preceding similar stimulus was followed by no depression of the reflex response. When, however, the peroneal nerve was stimulated strongly and brisk stretch of calf muscles produced, the usual action potentials of the C response were recorded from those muscles. These are shown and labelled in record 6 of Figure 8. In other areflexic patients, in whom only incomplete recovery from peripheral neuritis was revealed by considerable ataxia, no C responses were detected. Peroneal nerve shocks induced unchecked flinging movements in dorsiflexion rather than the responses described above. Seemingly then, detectable C responses to brief stretch were a necessary basis for normal locomotion, regardless of whether Group I fibre activity was discernible or not.

DISCUSSION

There can be little doubt that the reflexly-produced C responses described in this communication were due to stretch of calf muscle. They did not occur in its absence. It is equally evident that the rising phase of the stretch which caused the response was one which lasted for a considerable period of time. It certainly was not "brief" in the sense in which the adjective was used by Lloyd (1943). It lasted, in fact, for the contraction time of the dorsiflexor muscles. This was probably, then, little longer than the duration of the contractions and stretches used by Granit (1950) in cats, which lasted from 25 to 100 milliseconds.

Stretch caused in this fashion was followed by certain changes in excitability of the neurones which provided motor innervation to the same muscles. When this motoneurone excitability was tested by a volley of Group I afferent impulses (the monosynaptic reflex) during the arrival of the earliest components of the discharge from muscle, it was found enhanced (Fig. 6). Similar facilitation was found in cats by Lloyd (1943) following stretches which lasted only a few milliseconds. This facilitatory effect was caused by afferent impulses in Group I fibres which had been activated by the stretch. Since similar facilitation has been observed in man (Magladery, Teasdall, Park and Porter,

1951) following Group I volleys, it seems probable that the same cause applied in this instance. It is interesting, despite this facilitatory mechanism associated with the early stages of stretch and electrically-produced Group I volleys, that no enhancement of a succeeding stretch reflex was ever detected (Figs. 3 and 4). Apparently, during the short period when facilitation was manifest, the testing afferent impulses from muscle were still too few or asynchronous to discharge motoneurones. The receptor endings in cats with the lowest threshold are muscle spindles (Lloyd, 1943; McCouch, Deering and Stewart, 1950; Granit, 1950) and to these has been assigned the source for Group I fibres (Lloyd, 1943), and hence for the facilitatory effects. No comparable data exist for man but, from the close analogy already indicated, it seems quite likely that such should be the case.

More striking in these experiments, however, has been the profound depression of motoneurone excitability which occurred during and after the full response to stretch (Figs. 3, 5, and 6). This was also seen in cats by Granit (1950) and found increasingly prominent and lasting with greater intensities of the stretch. Such depression of reflex excitability was never found by Lloyd (1946) when motoneurones were conditioned by Group I afferent volleys. Likewise, it was not encountered in man when afferent discharges were confined to Group I fibres (Magladery, Teasdall, Park and Porter, 1951). To the contrary, it appeared when stimulus intensity was sufficient to discharge impulses in many Group II fibres and cause evident internuncial activity. Whereas the threshold overlap of these physiologically different fibre groups is considerable, yet it is clear that the size of Group II volleys increased with stronger stimulation. In the case of stretch as here described, all but the initial phases could readily be considered as strong stimulation. It is difficult indeed to explain the results of the present investigations on any basis other than that depression following stretch resulted from afferent impulses in Group II fibres and, therefore, likely through the intermediary of internuncial neurones.

This interpretation meets with no contradiction from the results of animal experiments. Neither Granit (1950) nor McCouch, Deering and Stewart (1950) have presented data to show that the autogenetic inhibition which they described rests on any other basis. Indeed Granit (1950) implied that a polysynaptic mechanism seemed quite probable. The receptor organs from which, in man, the inhibitory impulses arose, are completely unknown. In cats, however, increasing evidence points towards the Golgi tendon spindles (Granit, 1950; McCouch, Deering and Stewart, 1950). Since the present experiments can cast no light on that question, it seems well to simply assume that source as a possible one. It can be pointed out, however, that the inhibitory influences are in no way associated with conscious pain perception—either from skin or deeper structures (cf. Lloyd, 1943).

Here, then, are certain features of the afferent response to stretch in man.

In the early stages, the conditioning pattern resembles that caused by electrically-produced Group I volleys. Later, the profound inhibition is remindful of that following discharge of afferent impulses in Group II fibres. The first, rapid in onset and short-lived, seems eminently suited, as Granit (1950) suggested, to "speed up" contraction of muscle when it is weak. The more prolonged inhibitory influence, greater in the face of more intense stretch or contraction, may only introduce regulation through more complex pathways. If this is, indeed, the case, it is not irrelevant to ask how really important is this "speeding up" mechanism, and what is its role in normal total function. That certainly cannot be assessed at the present time. It may be pertinent, however, that in these investigations, two-neurone reflexes have only been recorded from certain large muscle groups in man. Furthermore, adequate stretch responses and apparently normal locomotion have been present in persons from whom, even in those large muscles, no monosynaptic reflexes could be detected.

SUMMARY

Muscle stretch has been caused by strong stimulation of antagonistic muscles. This produced a myotatic reflex discharge to the stretched muscle. Evidence has been presented to show that the initial phases of stretch activated Group I fibres and discharged monosynaptic reflexes. Later phases were probably subserved by Group II fibres and polysynaptic pathways. That the latter alone may afford sufficient basis for normal locomotion has been indicated by studies of persons from whom no monosynaptic activity was detectable.

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MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Monday, March 12, 1951

Dr. Fisher: Ladies and gentlemen, the first paper on the program this evening is by Dr. S. P. Asper and Dr. E. S. Wing, Jr., and will be presented by Dr. Asper.

PROPYLTHIOURACIL IN HYPERTHYROIDISM

During the past four years the Thyroid Clinic of The Johns Hopkins Hospital has been engaged in a study concerning the effectiveness of propylthiouracil in the treatment of hyperthyroidism. Since hyperthyroidism may occasionally be self-limited, and further, since propylthiouracil is effective in controlling the disease, it was deemed worthwhile to evaluate prolonged propylthiouracil therapy as a possible means of inducing permanent medical remission.

Two hundred and three hyperthyroid patients have been treated with propylthiouracil; 87 of these have taken the drug continuously for one year or longer. Propylthiouracil was found to ameliorate hyperthyroidism in 95 per cent of the patients receiving dosages of 300 mg. daily; smaller dosages were proportionally less effective. Response was slow, and was most satisfactorily followed on a clinical basis, although pertinent laboratory studies were done at intervals. The basal metabolic rate fell to normal range within 100 days of therapy. In patients with a marked weight loss associated with the onset of the disease, there was uniformly a rapid initial weight gain with treatment. Seventy-eight per cent of the lost weight was regained within the first six months of therapy.

The serum cholesterol rose sharply during treatment. Prior to treatment the serum cholesterol averaged 182.7 mg. % in 48 patients whereas the serum cholesterol averaged 246.4 mg. % after two months of treatment and 264.4 mg. % after 12 months of continuous treatment. In fourteen of these patients the serum cholesterol after one year of treatment ranged from 300 to 400 mg. %; this elevation of the cholesterol may represent over-treatment although no other manifestations of hypothyroidism were evident.

Twenty-four (50%) of 48 patients treated continuously for one year or longer have remained well after discontinuance of therapy; whereas the others experienced a relapse usually within six months after cessation of treatment. Generally prediction of ultimate remission or relapse in any given patient was not successful. However, remission was more likely to occur in those patients with mild hyperthyroidism and small diffuse goiter who were reliable in taking the drug. None of three patients with nodular goiter, 23 (56.1%) of 41 patients with diffuse goiter, and one (25%) of 4 patients with recurrent hyperthyroidism after previous thyroidectomy relapsed after cessation of prolonged therapy.

In 80 patients with diffuse toxic goiter the gland increased in size in 5 per cent, remained unchanged in 35 per cent, and definitely decreased in 60 per cent during prolonged therapy. In 21 of the 48 patients having a decrease in goiter size, the thyroid returned to normal size or became impalpable.

Exophthalmos significantly increased in 10 per cent of the patients with diffuse goiter but in no instance progressed to a malignant stage. Inadequate control of hyperthyroidism with propylthiouracil or concomitant administration of strong solution of iodine (lugol's solution) was present in the patients showing progression of exophthalmos.

Toxicity to propylthiouracil was infrequent. In 14 patients leukopenia without granulopenia was found on one or more occasions. In 12 other patients leukopenia with slight granulopenia occurred transiently. In none of these was therapy discontinued, but close

observation of the hematological status was maintained. In one patient with persistent granulopenia an examination of aspirated marrow showed normal morphological findings and distribution of the various types of marrow cells.

One patient developed agranulocytosis due to propylthiouracil. The marrow showed "maturation arrest." After cessation of therapy granulocytes returned to the peripheral blood and the patient recovered.

Two patients developed urticaria and one a collagen vascular disease-like state. All recovered when administration of the drug was discontinued.

Despite experimental evidence obtained by Malcolm, et al (Brit. J. Exp. Path., **30**, 17, 1949) that prolonged antithyroid therapy produces parathyroid hyperplasia in rats, no alteration of serum calcium, phosphorus, or alkaline phosphatase was found in 28 patients treated on an average of 2.4 years with propylthiouracil.

Papillary infolding of the acinar epithelium characterized the histological picture of the thyroid in patients long treated with propylthiouracil. No cancerous lesions are known to have developed in conjunction with prolonged therapy in these patients.

Control of hyperthyroidism with propylthiouracil was especially gratifying in patients with serious complicating disorders, such as hypertension, heart failure, asthma, diabetes, etc. No contraindication to prolonged therapy was apparent. Propylthiouracil appeared to be a safe and effective therapy for hyperthyroidism.

Dr. Fisher: Dr. Asper's paper is open for discussion. Dr. Thomas.

Dr. H. M. Thomas, Jr.: As far as I know, this is the largest group of patients that has been treated with propylthiouracil; they have been treated longer than any other reported group and for this reason Dr. Asper's findings are particularly significant. There are a great many interesting points, but two struck me particularly.

One was the change in the size of the gland. As far as I know, no other group of cases has been reported in which as many of the cases experienced a return to normal in the size of the palpated thyroid gland. I'd like to ask Dr. Asper if he thinks that in those cases in which the gland did not change much in the first two years or more of treatment and then, in the course of a few months, returned to normal in size—whether he thinks that at that time possibly the spontaneous cure of the disease took place while it was being held in remission by the propylthiouracil, and possibly at that time the overproduction of the thyroid-stimulating hormone ceased to occur, and the patients thereafter might have been considered cured.

The other point I was particularly interested in, and which I think may have real significance, is the exophthalmos. If the patients treated with propylthiouracil, as Dr. Asper showed, do not develop any increase in the exophthalmos, and if the progressive exophthalmos is actually prevented, then this is a very significant finding.

The reported increase following surgical thyroidectomy actually isn't very great, and in the 233 cases Dobyns reported, increase was fairly soon after thyroidectomy and only averaged 1.25 mm, so that the actual increase in the usual case is not very great, is more in cases of post-operative myxoedema, usually subsides in a matter of months, and it is only the unusual case that has severe exophthalmos. Dobyns has reported one case that started severe progressive exophthalmos during treatment with thiouracil, so I think that possibly—since this unusual type of severe progressive exophthalmos occurred only once in every thousand cases of hyperthyroidism treated at the Lahey Clinic—it is too soon to say that propylthiouracil does prevent the occurrence of this condition.

I believe, on the contrary, that in certain cases the exophthalmos actually increases

while under treatment with propylthiouracil. Some of you may remember the case of malignant exophthalmos shown in Staff rounds several weeks ago. During pre-operative preparation with propylthiouracil this patient's exophthalmos increased 3 mm. on each side. In cases of exophthalmic opthalmoplegia if the exophthalmos does not increase under treatment with propylthiouracil it has been our experience that thyroidectomy can be performed without precipitating progressive exophthalmos.

I think this is an extremely interesting series and I certainly am looking forward to further reports of the long-term treatment which Dr. Asper is doing.

Dr. Futcher: I'd like to ask Dr. Asper for what cases of hyperthyroidism he prefers propylthiouracil—what cases he feels are ideal for treatment by that drug?

Dr. Fisher: Is there any other discussion?

Dr. Wilkins: Our experience in hyperthyroidism in childhood is quite limited, but I think it should be mentioned here, as it confirms Dr. Asper's findings in every respect. We have had only twelve cases of hyperthyroidism since we began using propylthiouracil in 1946. We have not had a thyroidectomy performed during this time. Every case has been very well controlled. Three have remained in remission after discontinuing all therapy. The others are still under treatment and in good condition.

We agree entirely with Dr. Asper in regard to the very great importance of carrying out treatment over a long period of time, probably as long as three years, and then of withdrawing it gradually. We usually start with a dose of 300 mg. of propylthiouracil daily, the same as in adults. The subsequent regulation of the dosage at the euthyroid level, I think, requires a bit of skill, as in childhood especially it is of importance to maintain euthyroidism instead of producing hypothyroidism.

I would question whether some of the cases that Dr. Asper reported as having the high cholesterol under treatment—cholesterols up around 350 or 500 mg. %—might not be somewhat hypothyroid. It is our experience, watching carefully circulatory changes and such things, that the high cholesterol which we frequently see has indicated somewhat overdosage.

Dr. Fisher: Are there any other questions or discussion?

Dr. Rich: Mr. Chairman, I would like to ask Dr. Asper—I may have missed it—whether the level of the metabolic rate before the patients were treated bore any relation to whether or not remission occurred; and also, in relation to the sensitivity that develops, whether there is any evidence that patients who develop sensitivity require larger doses of propylthiouracil, since the development of antibody tends to reduce the efficacy of therapeutic substances. While the administration of sensitizing drugs is now stopped when evidences of hypersensitivity appear, I wonder whether formerly there were cases in which it appeared that larger doses were required after hypersensitivity developed. And finally, I am interested in the fact that the nodular goiters responded much better than the diffuse—I wonder whether the former were in patients who had been tending to have spontaneous remissions before treatment, the nodules representing perhaps the involution nodules that Dr. Rienhoff has shown to occur during remissions.

Dr. Scott: I would like to ask Dr. Asper on the basis of this study what he considers the present indications for subtotal thyroidectomy to be.

Dr. Fisher: Are there any other questions?

I am not sure whether Dr. Asper mentioned it in his summary, but I wonder how many cases needed thyroidectomy in this series?

Dr. Asper: In the patients treated for a long period of time, and who had a decrease in the size of the gland, we were not able to tell whether or not these patients would then undergo a spontaneous remission. We studied these patients carefully with that in mind. Many patients who had a decrease in the thyroid gland to normal size experienced a recurrence of the disease with discontinuance of therapy. Astwood, according to his recent publication, has had a similar experience. Our experience indicates that even though the gland decreases in size one cannot predict the patient will undergo permanent remission.

In the patients with high cholesterol, we were not able to tell that they were being overly treated with propylthiouracil, but it is true we were following our patients in the clinic where basal metabolic rates are not very reliable. Perhaps, if there were other methods of study, we might then determine that they were slightly overly treated.

Others have suggested, and particularly Sturgis, that the administration of propylthiouracil in large doses producing hypothyroidism during treatment is more likely to result in permanent remission. Sturgis' remission rate was 80 per cent. He believes patients kept in a hypothyroid state for a long time during treatment are more likely to undergo a permanent remission.

Our figures do not particularly indicate that—although we analyzed our patients—ultimate remission or relapse could be predicted on the basis of the initial basal metabolic rate. However, those with later recurrence were, on an average, 15 per cent higher initially than those who had a permanent remission. So, it appears that patients with a mild hyperthyroidism are more likely to experience a remission than those with a more severe hyperthyroidism.

We are not able to say much about the patients with nodular goiters, because there are only three in this group. We were, however, rather surprised by our own experience in these three patients with nodular goiters who appear to have a permanent remission. From cases published in the literature, this is of interest, as most authors have reported that hyperfunction of nodular goiters tends to recur after discontinuance of therapy. We, of course, have a considerable degree of open-mindedness about the efficacy of the total treatment, since it is well known that patients who have had subtotal thyroidectomies which were apparently successful may have recurrence of hyperthyroidism five to ten years later. Our patients have gone only two or three years following treatment in the longest instance, and this is not long enough to give satisfactory figures.

We did not have any prearranged plan for testing the various therapeutic schemata. In the patients who were treated early in this series, most were given 100 to 200 mg. daily and most of those prepared for subtotal thyroidectomy. We did not know the toxicity of propylthiouracil, so dosage was low and most of them were prepared for surgery. We are not able to say, then, on any real scientific basis, what the best plan of treatment is.

We do not have any prearranged plan for sending patients for surgery. It is difficult to treat patients on an out-patient basis with propylthiouracil. It takes a great deal of cooperation on the part of the patient taking pills day in and day out. But we feel that any patient who lives in Baltimore and is willing to come in regularly to the clinic and get the propylthiouracil pills—they are supplied by Lederle Laboratories—is a suitable candidate for prolonged therapy. We have, however, certain patients with ideal contraindications for operation: cardiac disability, diabetes, pregnancy, etc. We do not intend to suggest that patients with nodular goiters should not have subtotal thyroidectomy. We felt it would be

worthwhile to study the prolonged use of propylthiouracil. So in the last three years, the long-term patients referred to surgery have been those who no longer wished to take the drug, or who were unreliable and got tired of taking the pills, of whom there have been only four patients.

Dr. Fisher: The second paper deals with a related hormone. It is by Dr. W. H. Carnes, Dr. P. S. Rubin, and Mr. D. S. Bernstein. Dr. Carnes will give the paper.

REABSORPTION OF BONE MATRIX INDUCED BY PARATHYROID HORMONE

A clear distinction has been provided by several investigations in the past few years between the effect of parathyroid hormone on renal tubular excretion of phosphate on the one hand the the production of bone reabsorption ("osteitis fibrosa") on the other. The osseous effects of the hormone have been produced in nephrectomized animals. Direct homologous transplantations of parathyroid glands have produced local reabsorption of bone indicating a direct action of the hormone on bone. It becomes appropriate, therefore, to re-examine the entire conception of the means by which bone reabsorption is effected. The formerly favored explanation, in terms primarily of solution of bone mineral by mass action equilibrium, loses force in view of the fact that negative phosphorus balance is unessential for the effect. Even when solution of bone salt is considered the initial step in the process, the practically simultaneous reabsorption of bone matrix must be granted and accounted for. No direct evidence has ever been adduced that solution of bone salt is the initial step. Experiments are described which show that bone matrix, ostensibly free of mineral, is reabsorbed in precisely the same manner as is normal bone under the influence of parathyroid hormone. Young rats, after 4 weeks on a rachitogenic diet low in calcium and phosphorus, have been treated with large doses (250 U.S.P. units per day) of Lilly parathyroid extract. Rapid reabsorption of the metaphyseal chondro-osteoid tissue and a typical osteitis fibrosa result which is quite comparable to that in normal rats treated similarly. Examination of histological sections of undecalcified bones at intervals of 8 to 72 hours after beginning treatment show progressive diminution in the amount of osteoid tissue and typical "lacunar reabsorption" of this non-calcified matrix may be seen in abundance. Identical effects are produced on the non-calcified osteoid matrix of fracture callus. These observations suggest that the ultimate mechanism of bone reabsorption induced by parathyroid hormone is independent of the mineral component of the bone and should be sought in the realm of an effect on bone matrix.

Dr. Fisher: The paper is open for discussion.

Dr. Wilkins: I would like to ask one question. How would you explain the fact that in parathyroid adenoma under certain conditions serum calcium changes and phosphorus may be present and osteitis fibrosa may not occur? Last year we saw a case of parathyroid adenoma at Sinai Hospital in which bone biopsy showed no changes whatever.

Dr. Fisher: Are there any other questions?

Dr. Rich: I would like to say that to those of us raised on the idea that everything that happens in the bones following the administration of parathyroid hormone, or overactivity of parathyroids, is due primarily to the withdrawal of minerals from the bone, whether by loss of phosphorus from the kidney or by direct demineralization of the bone—to those of us raised on that idea, the idea that the primary effect may be on the matrix is certainly a

very interesting and novel one. I think that if it were possible to work with a rickety bone that had no calcification whatever, the unequivocal test of this would be a great deal easier. That, as Dr. Carnes said, is hardly possible, though the amount of calcification can be reduced to very low level. I think that the most persuasive slides were those of the healing fractures, in which the calcification in the osteoid is reduced to a very, very low level, and in large areas not present at all, yet in those areas the resorption of the matrix seemed to take place under the influence of parathormone.

Dr. Futcher: Dr. Fisher, in 1935, when there was considerable interest in the part played by the kidney in mediating the action of parathyroid hormone on the serum calcium, Dr. Read Ellsworth took the lead in conducting some experiments with a few dogs in which the kidneys were removed and parathyroid extract administered. The serum calcium rose in those animals considerably more than the slight increase shown in controls to whom the hormone was not administered. Recently I think Pitts has some experimental evidence showing that in animals parathyroid hormone does not influence the tubular resorption of phosphorus, suggesting that there may be some prerenal mechanism in the increased excretion of phosphorus following the administration of the parathyroid hormone. I think it is also true that in about 1943 Dr. Albright came out with a report indicating that there was a local effect of parathyroid extract on the bone in nephrectomized animals. I believe he supplements his phosphorus excretion theory with evidence of a direct local effect of parathyroid extract on bone.

Dr. Follis: I think the evidence, part of which Dr. Carnes mentioned, that of Barnicot in England, and workers in William Bloom's laboratory in Chicago, indicates pretty clearly that there is a local effect of parathyroid hormone on the bone. Experiments have been carried out using homologous implants of parathyroid gland beneath the periosteum of the skull and, as Bloom has shown quite conclusively, there is rarefaction of the bone around the implants. The implantation of other endocrine tissues, such as the thyroid, pancreas, etc., doesn't produce such a change. So that I think there are probably two mechanisms which have to do with parathyroid activity; namely, the local one shown in England and, secondly, from the work which has gone before, and some unpublished work which Dr. Philip Handler has been carrying out at Duke University, there is a very definite effect on the excretion of phosphorus by the kidney in parathyroid hormone hyperactivity.

Dr. Fisher: Is there any other discussion? Dr. Carnes.

Dr. Carnes: I am aware of Dr. Ellsworth's and Dr. Futcher's work on this mechanism of action some years ago. They were among the first to show that parathyroid extract did have some effect in nephrectomized animals. The object of their study was the serum calcium of the animals rather than the bone. I had intended making some mention of this if I were given an opportunity. It has been amply confirmed although there have been several people, from time to time, who have not been able to get the result. I think that is easily explained by the fact that very large rises in serum calcium are not possible in the nephrectomized animal and Stoerk has shown that the effect of the extract on animals that are both parathyroidectomized and nephrectomized is much more dramatic. The relationship of this kind of observation in the nephrectomized animal to the effects on serum and urinary phosphorus in the intact animal is more difficult to state. Pitts had denied that the renal tubular reabsorption of phosphate is specifically affected by parathyroid hormone, although I believe that he has stated that glomerular filtration is increased, which might explain

the increased phosphate loss. That is a subject I have steered clear of purposely, because I find it difficult to interpret all the findings that have been reported.

I have been prepared for your question, Dr. Wilkins, about the finding of normal bones by biopsy in patients who have chemical evidence of hyperparathyroidism and, indeed, who have had parathyroid tumors. Dr. Follis has needled me about that a good bit and I don't know the answer to it, but we are giving it our energetic consideration at the present time.

Dr. Fisher: The last paper is by Drs. J. R. Krevans, C. L. Conley, and C. R. Barrows, Jr. It will be presented by Dr. Krevans.

OBSERVATIONS ON THE ABSORPTION AND EXCRETION OF VITAMIN B_{12}

Crystalline vitamin B_{12} was given parenterally to normal individuals and to patients with treated and untreated pernicious anemia. Urine collected following injection was assayed microbiologically for B_{12} activity. Following the intramuscular injection of 25 micrograms or less of vitamin B_{12} there was no measurable increase in the B_{12} activity of the urine. When 100 micrograms were injected intramuscularly the B_{12} activity of the urine collected in the first 8 hours accounted for approximately 40 per cent of the injected vitamin. There was little additional excretion of vitamin B_{12} after the first 8 hours. When 500 micrograms or more of B_{12} was given parenterally approximately 100 percent of the injected vitamin could be accounted for in the urine in the first 8 hours. There was no measurable difference in the urinary excretion of vitamin B_{12} of normal individuals and of patients with pernicious anemia. The administration of single oral doses of vitamin B_{12} in amounts as large as 10,000 micrograms was not followed by a measurable increase in the B_{12} activity of the urine in normal individuals or in patients with pernicious anemia. Nevertheless 4 patients with pernicous anemia in relapse showed striking hematologic responses when given single oral amounts of vitamin B_{12}. Patients receiving 3000 or more micrograms had complete hematologic remissions without further therapy. The absorption and excretion of vitamin B_{12} was studied further using B_{12} containing radioactive Cobalt 60. Five micrograms of the labelled vitamin were administered orally to a normal subject. Feces excreted in the following 4 days was homogenized, ashed, extracted with α-nitroso-β-naphthol, and electroplated on copper discs from a saturated solution of ammonium oxalate. The radioactive Cobalt recovered accounted for 4.8 of the 5 micrograms administered. These observations indicate that vitamin B_{12} is poorly absorbed from the normal gastro-intestinal tract.

Dr. Fisher: The paper is open for discussion.

Dr. Conley: We embarked upon this project with considerable enthusiasm. At first we observed that vitamin B_{12} was rapidly excreted in the urine when administered parenterally both to normal individuals and to patients with pernicious anemia. We anticipated that normal individuals receiving B_{12} orally would excrete large amounts in the urine. We further anticipated that patients with pernicious anemia would not absorb the vitamin and therefore would not excrete it in the urine. We expected that this procedure would greatly facilitate the study of the nature of intrinsic factor. It also seemed possible that the procedure could be utilized as a diagnostic test in those individuals with pernicious anemia who had no anemia at the time of examination. We are disappointed, therefore, with the results which we have obtained, but think, nevertheless, that the results are of some interest.

Dr. Chow: Dr. Krevans, I wish to make the following comments on your excellent discussion on the utilization of vitamin B_{12} by man. Firstly, our experiments on animals, likewise, demonstrated that the oral administration of vitamin B_{12} to rats or dogs did not cause the appearance of its microbiological activity in the urine, whereas most of the administered B_{12} was found in the fecal matter. In the second place, we have administered parenterally vitamin B_{12} containing radioactive Co^{60} to vitamin B_{12} deficient and vitamin B_{12} saturated animals. Their urine samples were collected and assayed for vitamin B_{12} content by means of microbiological activity and activity of radioactive Co^{60}. Our preliminary results suggested a marked difference in the ratios of the two activities in the samples of urine of the two types of rats; the ratio, being higher for the saturated rats than for the deficient rats. Is it not plausible that similar study in man might provide us with a basis for that estimation of B_{12} reserve?

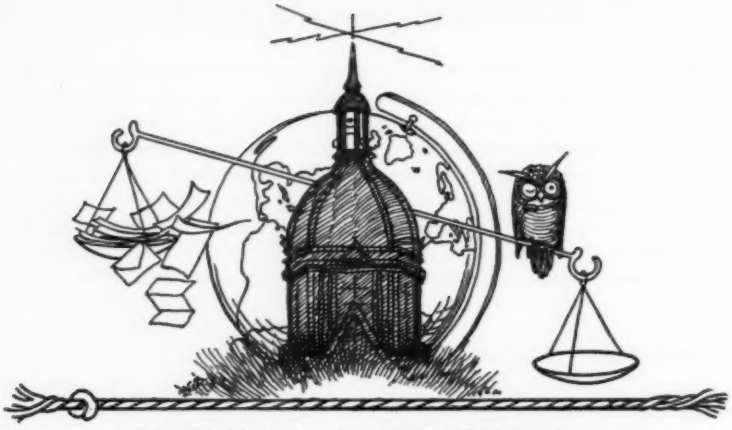
Dr. Rich: What happens to the radioactive B_{12} injected intravenously?

Dr. Fisher: Are there any other questions? Dr. Krevans.

Dr. Krevans: Well, unfortunately both questions have no answer as yet. As far as the first is concerned, Dr. Chow, actually we have completed one experiment, the one I mentioned in which 25 micrograms of vitamin B_{12} were given intramuscularly to a patient with pernicious anemia. We detected radioactivity equivalent to 0.5 micrograms of B_{12} in the patient's urine excreted in the first 24 hours following injection. Microbiological assays on the same urine failed to detect any B_{12} activity. The radioactive recovery indicates a concentration of approximately 0.5 millimicrograms per ml. which is certainly within the limits that could be detected by the microbiological method. However, we do have frozen urine specimens on all our other experiments and if your laboratories are anxious to do these studies, we would be very happy to have them done.

Dr. Rich, that hasn't been done yet. We started out rather hesitantly. We knew we were dealing with a substance with a long half-life and we wanted to be sure in every case that we were not exposing our subjects to any danger. I think now it is certainly very feasible to administer the B_{12} intravenously and we contemplate doing this in the near future.

Dr. Fisher: Thank you very much.
The meeting is adjourned.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of members of the Editorial Board of this Bulletin)

Operations of General Surgery, 2nd edition. By THOMAS G. ORR. 890 pp. $13.50. W. B. Saunders Co., Philadelphia, Pa.

This is essentially an atlas of surgical operations and a text accompanies the illustrations. The pictures are excellent; most represent wise borrowings from previously published books and journals.

Perhaps too much ground is covered too scantily. In addition to the operations of "General Surgery" narrowly defined, there are chapters on plastic, orthopedic, brain, genito-urinary and gynecological surgery. This wide spread makes intensive coverage of any subject impossible despite the 864 pages and the 721 figures. It may be fair to ask if any but intensive coverage of technical surgical procedures is permissible. Is it proper and is it well, in one text, to outline all sorts of surgical operations on the assumption that the same individual will close cleft palates, excise varicoceles, suspend uteri, decompress the brain subtemporally, reinforce a puny anal sphincter, enter aneurysms, transplant tendons, plate and graft fractures, excise the pancreas and create or close communications between this and that? Granting in one individual technical mastery, the less spectacular trait in judgment of election cannot be so transmitted. It seems fair mildly to criticize putting so many subjects in a book.

A great deal of thought and work has gone into the preparation of this volume and it should prove useful, especially at the level of the junior House Surgeon or the physician who is forced, on occasion, to work outside his proper field.

W. E. G.

Thoracic Surgery. By RICHARD H. SWEET. 345 pp. $10.00. W. B. Saunders Co., Philadelphia, Pa.

In this small volume the author has drawn heavily on his own extensive experience with the surgery of the chest to present a detailed coverage of the technics of thoracic surgery.

As stated in the preface the book "is based upon the concept that any properly qualified surgeon can acquire with relative ease a satisfactory proficiency in thoracic surgery by employing the technics herein described." Beginning with introductory chapters on surgical anatomy of the thorax, general technical considerations and thoracic incisions, the author presents descriptions of operations on the thoracic wall and operations concerning the pleural cavity. Following in order are chapters on the lung; the mediastinum, including heart and great vessels; two chapters on surgery of the esophagus; a description of abdominal operations performed through thoracic incisions and finally, the surgery of the diaphragm. The lucid and concise technical discussions are profusely illustrated by sketches of operative approaches, exposures, dissections, suture technics and anatomical diagrams.

This is an instructive book. The procedures which are described have the practical background of Dr. Sweet's wide experience in thoracic surgery. The book is primarily designed as a technical treatise on surgery of the chest and as such it is a valuable one. However, one cannot escape the feeling that it would be more valuable if its scope were extended to include some discussion, even though brief, of the disorders for which the various operative procedures are done together with an evaluation of results. The absence of a bibliography and the lack of reference to other contributors in the field are serious deficiencies.

H. W. S., Jr.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. Vol. 1. By Arthur Steindler. 302 pp. $7.50. Charles C Thomas Co., Springfield, Illinois.

This book represents the first of a projected series of four volumes to contain lectures on orthopedic subjects. Volume I begins with a section on propedeutics (defined by the author as "preliminary to the teaching of orthopedic surgery"), in which consideration is given to body symmetries, joint motion, contractures, gaits and the interpretation of pain in orthopedic surgery. The second section is devoted to congenital deformities and disabilities and presents observations on the basic concepts of malformation, defects due to the disturbance of bone growth, and regional congenital deformities, such as those of the trunk and the extremities, the talipes and congenital dislocation of the hip. Without being exhaustive compendia, the lectures are meaty presentations of each subject and incorporate ideas gathered in a wide survey of the literature as well as the personal observations of the author and his co-workers. The author's analysis of the processes involved in the evolution and treatment of various conditions is quite interesting. The advanced student of orthopedics will find the presentations stimulating. The practicing orthopedist can obtain a valuable refresher course in the study of these lectures.

I. W. N.

Blood Clotting and Allied Problems. Trasactions of the Third Conference, January 23–24, 1950. Edited by Joseph E. Flynn. 224 pp. $3.00. Josiah Macy, Jr. Foundation, New York.

The annual conferences sponsored by the Macy Foundation make possible informal round table discussions by a select group of leading investigators. In the field of blood coagulation, so many diverse and seemingly incompatible concepts exist that these conferences provide a unique opportunity for investigators to correlate and integrate their experimental observations in an effort to arrive at explanations and hypotheses acceptable to all. It is disappointing, therefore, to find that no attempt was made to integrate the observations of the numerous workers. On the other hand, the members of the conference tended to defend unrelentingly their own views, while often displaying unconcealed contempt for the work of their fellow investigators.

At the conference, several subjects of rather general interest were discussed. These included the effectiveness of vitamin K preparations in overcoming the hypoprothrombinemia induced by dicumarol, and experimental and clinical studies on the newer anticoagulants phenylindanedione, tromexan and paritol.

C. L. C.

Klinische Pathologie der Blutkrankheiten. By RUDOLPH SCHOEN and WALTER TISCHENDORF. 521 pp. DM. 57. Georg Thieme Verlag, Stuttgart.

This is a well written discussion in the field of hematology and is worthy of study by any physician interested in that specialty.

There are nine sections ranging from topics on morphology of various blood cells, pathological changes in blood diseases, techniques of routine studies, the different types of anemia, conditions characterized by increased bleeding tendencies, leukopenia, leukemia, leukemoid reactions and familial blood dyscrasias.

There are some minor errors. Autopsies in acute porphyria may show striking changes in the central nervous system and peripheral nerves as well as celiac ganglia. Whether barbiturates play an etiological role in some cases of porphyria is debatable. Folic acid is not good therapy in cases of pernicious anemia.

The authors wisely draw conservative conclusions about the use of folic acid antagonists in the treatment of leukemia.

The bibliography is up-to-date and as a general rule contains the more important and key references in the topics discussed. However, the cross indexing is very poor.

P. F. W.

The Low Fat, Low Cholesterol Diet. By E. VIRGINIA DOBBIN, HELEN F. HOFMAN, HELEN C. JONES, LENORE LYON and CLARA-BETH YOUNG. Introduction by THOMAS P. LYON AND JOHN W. GOFMAN. 371 pp. $3.45. Doubleday & Co., New York.

This is a manual devoted entirely to the low fat, low cholesterol diet. It is written at the level of the lay consumer of the diet and is a very practical guide for the preparation and maintenance of such a dietary program. There has been accumulated a tremendous amount of information that should be helpful to physicians and dieticians and housewives who might be supervising patients on a low fat, low cholesterol diet.

At the present time, there are many series of patients being studied to ascertain the effect of such dietary restrictions on atherosclerosis. This is a controversial subject and the value of such diets has by no means been established. To those research workers in this field this diet manual should prove a very useful tool, in helping to keep their study subjects on such a program. The price of the book is low enough, so that almost any patient could own a copy for home use.

M. L. S.

Toxaemias of Pregnancy. Human and Veterinary. A Ciba Foundation Symposium. Edited by JOHN HAMMOND, F. J. BROWNE and G. E. W. WOLSTENHOLME. 280 pp. $4.50. The Blakiston Co., Philadelphia, Pa.

The decision of the Ciba Foundation to publish the proceedings of the symposium on toxaemias, held under its auspices in London in the Spring of 1950, has produced in one volume, the most modern thought concerning this syndrome. There are thirty-one different papers, including three of summary nature written by some of the world's outstanding investigators in this field. Of particular note are those of Dieckmann relative to salt metabolism; of Sommerville on placental sex hormones; Sheehan on pathological changes in eclamp-

sia and van Bouwdijk Bastiaanse on the ischemia of the uterus as a causative factor in toxaemia. The articles on diseases in cattle simulating eclampsia are of great interest and when read simultaneously with the human material seem to differentiate clearly the parturiate diseases of animals from human toxaemia.

Although much of this material is available in the world's literature, its presentation here in one small volume makes it a must for the obstetrician, or for that matter, any investigator interested in hypertension.

L. M. H.

Researches in Binocular Vision. By KENNETH N. OGLE. 345 pp. $7.50. W. B. Saunders Co., Philadelphia, Pa.

This book presents new research material and summarizes certain concepts of the sensory aspects of binocular vision. The work which was done at the Dartmouth Eye Institute at Hanover, New Hampshire is described in detail. The first part of the book deals with the organization and sensory cooperation of the two retinae. After a brief discussion of the anatomy of the visual pathways there is a consideration of objective and subjective space. This leads into a consideration of the horopter. The second part of the book deals with fusional processes in binocular single vision. After a brief consideration of the fusion reflex, Panum's fusional areas are discussed. A consideration is then made of fixation disparity, fusion from peripheral retinal stimuli and cyclofusional eye movement. The third portion of the book deals with the problems created in binocular vision when changes are made in the relative magnification in the images of the two eyes. The last portion deals with the experimental and theoretical basis for aniseikonia.

W. C. O.

BOOKS RECEIVED FOR REVIEW

The Bases of Human Behavior. A Biologic Approach to Psychiatry. By LEON J. SAUL. 150 pp. $4.00 J. B. Lippincott Co., Philadelphia, Pa.

Cancer as I See It. By HENRY W. ABELMANN. 100 pp. $5.00. Philosophical Library, New York.

A Classified Bibliography of Gerontology and Geriatrics. By NATHAN W. SHOCK. 599 pp. $15.00. Stanford University Press, Stanford, California.

Dimensional Analysis for Students of Medicine. By HAROLD A. ABRAMSON. 41 pp. $1.00. Josiah Macy, Jr. Foundation, New York.

The Doctor. His Career. His Business. His Human Relations. By STANLEY R. TRUMAN. 151 pp. $3.00. The Williams & Wilkins Co., Baltimore, Md.

The Education of Nursing Technicians. By MILDRED L. MONTAG. 146 pp. $2.50. G. P. Putnam's Sons, New York.

An Introduction to Universal Serologic Reaction in Health and Disease. By REUBEN L. KAHN. 158 pp. $3.50. The Commonwealth Fund, New York.

Josiah Macy, Jr. Foundation, 1950, Twentieth Anniversary Review. 110 pp. Josiah Macy, Jr. Foundation, New York.

A Medical History of Persia and the Eastern Caliphate. By CYRIL ELGOOD. 617 pp. $10.00. Cambridge University Press, New York.

Medical Neuropathology. By I. MARK SCHEINKER. 372 pp. $10.00. Charles C Thomas, Springfield, Illinois.

Methods of Vitamin Assay, 2nd edition. Prepared and edited by the Association of Vitamin Chemists, Inc. 301 pp. $5.50. Interscience Publishers, New York.

The Microkaryocytes. The Fourth Corpuscles and their Functions. By K. G. KHOROZIAN. 969 pp. $12.00. Meador Publishing Co., Boston, Massachusetts.

Paracelsus. Magic into Science. By HENRY M. PACHTER. 360 pp. $4.00. Henry Schuman, Inc., New York.

Trends in Gerontology. By NATHAN W. SHOCK. 153 pp. $2.50. Stanford University Press, Stanford, California.

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